Uterine artery embolization

de Bruijn, A.M.

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UTERINE ARTERY EMBOLIZATION

FOR FIBROIDS AND ADENOMYOSIS

ANNEFLEUR DE BRUIJN

Uterine artery embolization for fibroids and adenomyosis
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FOR FIBROIDS
AND
ADENOMYOSIS

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CONTENTS

1

Introduction

GENERAL INTRODUCTION

The general introduction discusses the background of this thesis and provides insight in epidemiology, symptomatology, diagnosis and treatment of uterine fibroids and adenomyosis.

UTERINE FIBROIDS

Uterine fibroids are common benign tumors originating from neoplastic transformation of smooth muscle cells in the uterine wall [1] Approximately 20-40% of women are affected in their reproductive age [2]. Lifetime prevalence of patients with uterine fibroids is high and has been reported up to 77%, however many of these patients are asymptomatic [3]. Most uterine fibroids are located in the body of the uterus, uterine fibroids located in the cervix are rare, ranging from 0.9 - 8% of all uteri containing fibroids [4-6]. Symptoms associated with uterine fibroids are heavy menstrual bleeding, pain (dysmenorrhea) and bulk related symptoms [7].When non-invasive treatment options like oral contraceptives, levonogestrel intrauterine systems, progestins, coagulation stimulants, GnRH analogues, non-steroidal anti-inflammatory drugs fail and hysteroscopic resection is not an option, invasive surgical intervention like myomectomy or hysterectomy may be necessary.

ADENOMYOSIS

Adenomyosis is described as the benign presence of ectopic endometrial glands and stroma causing reactive hypertrophy of the smooth muscle fibers of the myometrium [8, 9]. The prevalence of adenomyosis is estimated to be 5%-8% in some studies, whereas others find even 40%-70% [10-12; 13]. Approximately one-third of women with adenomyosis are symptomatic [9]. Symptoms associated with the presence of adenomyosis are heavy menstrual bleeding, pain (dysmenorrhea) and an enlarged uterus. About 40%-50% of patients will suffer from heavy menstrual bleeding and 15%-30% of dysmenorrhea [10]. Fibroids are present in up to 55% of the patients diagnosed with adenomyosis. Therefore, it can be difficult attributing symptoms to one or the other [14, 15]. Although adenomyosis is usually diagnosed in women between 40 and 60 years of age, it is also described in young women in whom any surgery performed on the uterus might adversely affect child-bearing [16]. Among conservative therapies the levonogestrel intrauterine system is shown to be most effective in patients with symptomatic adenomyosis [17], other conservative such as oral contraceptives, progestins, coagulation stimulants, GnRH analogues and non-steroidal anti-inflammatory drugs could also be considered, however if conservative treatment fails no other

treatment options remain other than a hysterectomy, since adenomyosis cannot be removed surgically from the uterus.

UTERINE ARTERY EMBOLIZATION FOR FIBROIDS AND ADENOMYOSIS

UAE was first described as a treatment of symptomatic uterine fibroids in 1995 [18]. UAE is performed by the interventional radiologists in an angiography suite. Via a femoral approach a catheter is positioned into the uterine artery under fluoroscopy guidance. Embolization is then performed by injection of an embolic agent in order to block the vessels towards the fibroid. Since 1995 UAE was established as being a valuable treatment alternative for hysterectomy in many studies including several randomized controlled trials [19-26]. A Cochrane review based on these randomized controlled trials concluded that UAE for symptomatic fibroids is a safe alternative for surgery in terms of quality of life and treatment satisfaction rates [27].

Based on the positive results as reported in the randomized controlled trials in the treatment of uterine fibroids, UAE has been considered as a possible treatment option for adenomyosis. Favorable outcomes of UAE for adenomyosis have been reported in various case series, however randomized controlled trials are lacking [28-35].

CLINICAL PROBLEMS

UAE FOR UTERINE FIBROIDS

UAE for fibroids has been compared to hysterectomy in several RCT's. The results are clear: similar improvement in Health Related Quality Of Life (HRQOL) and lower costs against a secondary hysterectomy rate of 28.4% after 5 years of follow-up. First, uterine fibroids can cause symptoms until the onset of menopause. Therefore follow-up of trials evaluating treatment effect on uterine fibroids should be continued until the patients reached menopause. Only then an accurate estimation of clinical failures can be established. Second, UAE can be applied for special indications such as cervical fibroids. Since operative removal can cause severe problems during surgery UAE might be an alternative. No studies have been published on the effectiveness of UAE for this indication. Third, UAE was integrated as a treatment option on which patients should be counseled in the national Dutch guideline on heavy menstrual bleeding [36]. Since then no increment has been noted in the number of UAE procedures [37]. It is not known why this has not happened.

UAE FOR ADENOMYOSIS

Hysterectomy is a good and definite treatment option for adenomyosis. Hysterectomy is also considered to be a major surgical procedure with a long recovery time and possible long term sequalae. Furthermore, some patients wish uterus preserving options, even when conception is no longer desired. This justifies exploration of alternatives to hysterectomy such as UAE in the treatment of symptomatic adenomyosis. There has been some experience in case series on UAE for symptomatic adenomyosis [38]. However, long term follow-up is mostly not available and no randomized data are available.

ULTRASONOGRAHIC IMAGING IN DIAGNOSING ADENOMYOSIS

Until recently the diagnosis of adenomyosis depended on histology following invasive surgery. Because of the fact that only a small and selected group of women undergo hysterectomy, an accurate estimation of the prevalence of the disease cannot be established [39]. Nowadays, the introduction of imaging techniques such as transvaginal ultrasonography (TVUS) and Magnetic Resonance Imaging (MRI), has allowed non-invasive diagnosis of adenomyosis [40-43]. Ultrasonography is widely available in an office setting, it is relatively inexpensive, requires no preparation, has no contraindications and is relatively accurate in experts hands, and is therefore the imaging modality of first choice in gynecology [42]. However, concurrent fibroids can cause a challenge when diagnosing adenomyosis. It can be difficult attributing symptoms and imaging modalities to one or the other [14; 15; 44]. This could therefore cause some therapeutic problems, since patient management is often based on an ultrasound diagnosis only and surgical options between these two benign uterine pathologies differ. Even though a consensus statement was published describing myometrial lesions as seen using ultrasonography it does not provide a guideline for how to classify morphological types or extent of adenomyosis [44]. This stresses the importance of a uniform, reproducible and clinically relevant reporting system as well as a validation of ultrasound findings compatible with adenomyosis

AIM OF THE THESIS

This thesis consists of the following two parts;

PART I) Long term follow-up of and implementation of uterine artery embolization (UAE) for symptomatic uterine fibroids,

PART II) UAE as a treatment in patients with symptomatic adenomyosis and towards standardization of ultrasonography in adenomyosis.

The specific research questions in accordance with the two parts:

PART I)

1. What is the effectiveness of UAE in the treatment of symptomatic uterine fibroids 10 years after intervention in terms of satisfaction and HRQOL?
2. Is there an increase in UAEs after the new introduced guideline in 2013 and how does this effect the UAE/hysterectomy ratio?
3. What counseling preferences do gynecologists have concerning UAE?
4. What is the efficacy and safety of UAE in the treatment of patients with symptomatic cervical fibroids?

PART II)

5. What is the effectiveness of UAE in the treatment of symptomatic adenomyosis 7 years after intervention in terms of HRQOL, symptom severity and satisfaction rates?
6. What is the effect of UAE on symptomatic pure adenomyosis and adenomyosis combined with fibroids in term of symptom improvement and imaging outcomes?
7. How is a randomized controlled trial set up comparing UAE and hysterectomy in terms of HRQOL, complications during treatment, hospital stay, return to normal activities, recovery index, satisfaction with allocated treatment, patient preferences, sexual functioning, recurrence of complaints, re-interventions and imaging outcomes?
8. How should adenomyosis be assessed, classified and reported when diagnosing it on ultrasonography?

OUTLINE OF THE THESIS

PART I. UAE IN THE TREATMENT OF UTERINE FIBROIDS

CHAPTER 2 describes the 10-year outcomes of UAE compared with hysterectomy in the treatment of symptomatic uterine fibroids in the randomized EMMY trial (question 1).

CHAPTER 3 presents the results of UAE implementation in the treatment of patients with symptomatic fibroids in the Netherlands supported by number from annual hospital reports. Furthermore, it assessed the different aspects of UAE counseling, preference, difficulties and knowledge/awareness as reported by gynecologists working in UAE performing hospitals and non-UAE performing hospitals (question 2 and 3).

CHAPTER 4. describes efficacy and safety of UAE in the treatment of symptomatic cervical fibroids (question 4).

PART II. UAE IN THE TREATMENT OF ADENOMYOSIS AND TOWARD STANDARDIZATION OF ULTRASONOGRAPHY IN DIAGNOSING ADENOMYOSIS

CHAPTER 5 describes a seven-year clinical follow-up of patients with symptomatic adenomyosis treated with UAE (question 5).

CHAPTER 6 presents the results of a systematic review and meta-analysis of the available literature, evaluating treatment effect in patients with symptomatic adenomyosis (question 6).

CHAPTER 7 presents the design of the randomized controlled QUESTA (*Quality of Life after Embolization vs Hysterectomy in Adenomyosis)* trial. A trial comparing UAE and hysterectomy in the treatment of patients with symptomatic adenomyosis (question 7).

CHAPTER 8. presents a consensus based practical classification of adenomyosis on the basis of ultrasound findings developed by experts across the world (question 8).

PART III:
SUMMARY, GENERAL DISCUSSION AND CONCLUSION

CHAPTER 9 summarizes all our results categorized by subject. We discuss results from our trial in the context of current literature. Finally our conclusions are presented.

CHAPTER 10 provides a summary and conclusions in Dutch.

PART IV

List of publications, dankwoord en curriculum vitae.

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PART I

LONG TERM FOLLOW-UP AND IMPLEMENTATION OF UAE IN PATIENTS WITH FIBROIDS

2

Uterine artery embolization vs hysterectomy in the treatment of symptomatic uterine fibroids: 10-year outcomes from the randomized EMMY trial

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ABSTRACT

BACKGROUND

Since 1995 uterine artery embolization has been described as an alternative for hysterectomy in patients with symptomatic fibroids. Many studies including several randomized controlled trials established uterine artery embolization as a valuable treatment. These randomized controlled trials reported outcomes in terms of health-related quality of life, clinical outcomes, efficacy, and cost-effectiveness after 1, 2, and 5 years of follow-up.

OBJECTIVE

The purpose of this study was to compare clinical outcome and health-related quality of life 10 years after uterine artery embolization or hysterectomy in the treatment of heavy menstrual bleeding caused by uterine fibroids in a randomized controlled trial.

STUDY DESIGN

In all, 28 Dutch hospitals recruited patients with symptomatic uterine fibroids who were eligible for hysterectomy. Patients were 1:1 randomly assigned to uterine artery embolization or hysterectomy. The outcomes assessed at 10 years postintervention were reintervention rates, health-related quality of life, and patient satisfaction, which were obtained through validated questionnaires. Study outcomes were analyzed according to original treatment assignment (intention to treat).

RESULTS

A total of 177 patients were randomized from 2002 through 2004. Eventually 81 uterine artery embolization and 75 hysterectomy patients underwent the allocated treatment shortly after randomization. The remaining patients withdrew from the trial. The 10-year questionnaire was mailed when the last included patient had been treated 10 years earlier. The mean duration of follow-up was 133 months (SD 8.58) accompanied by a mean age of 57 years (SD 4.53). Questionnaires were received from 131 of 156 patients (84%). Ten years after treatment, 5 patients underwent secondary hysterectomy resulting in a total of 28 of 81 (35%) (24/77 [31%] after successful uterine artery embolization). Secondary hysterectomies were performed for persisting symptoms in all cases but 1 (for prolapse). After the initial treatment health-related quality of life improved significantly. After 10 years, generic health-related quality of life remained stable, without differences between both groups. The urogenital distress inventory and the defecation distress inventory showed a decrease in both groups, probably related to increasing age, without significant differences between study arms. Satisfaction in both groups remained comparable. The majority of patients declared being (very) satisfied about the received treatment: 78% of the uterine artery embolization group vs 87% in the hysterectomy group.

CONCLUSION

In about two thirds of uterine artery embolization treated patients with symptomatic uterine fibroids a hysterectomy can be avoided. Health-related quality of life 10 years after uterine artery embolization or hysterectomy remained comparably stable. Uterine artery embolization is a well-documented and less invasive alternative to hysterectomy for symptomatic uterine fibroids on which eligible patients should be counseled.

INTRODUCTION

Uterine artery embolization (UAE) was first described for the treatment of symptomatic uterine fibroids in 1995 [1]. Since then UAE was established as being a valuable treatment alternative for hysterectomy in many studies including several randomized controlled trials. These randomized controlled trials compared hysterectomy or myomectomy with UAE and found similar results in terms of health-related quality of life (HRQOL) after 1, 2, and 5 years of follow-up [2-9]. Earlier we reported on the results from the randomized EMMY (Embolization vs Hysterectomy) trial. These results contained data through 5 years after index procedure [3;6-16]. We compared clinical results [8], HRQOL outcomes [9] and menopausal symptoms [13] between embolization and hysterectomy. In the present study, we analyzed these results again, now 10 years after treatment.

METHODS

STUDY DESIGN

The full methods of this trial have been described earlier [6;8;9]. Here we describe the condensed methods. The EMMY study is a multicenter, randomized controlled trial, conducted in The Netherlands from 2002 through 2004. Five university hospitals and 29 general hospitals recruited patients. Patients with symptomatic uterine fibroids who visited the gynecological outpatient clinic were asked to participate in the trial. The following inclusion criteria had to be met: (1) premenopausal status, (2) diagnosis of uterine fibroids by ultrasonography, (3) heavy menstrual bleeding as the predominant symptom, (4) no other treatment option than hysterectomy, and (5) no wish to conceive in the future. The study was approved by the Central Committee Involving Human Subjects followed by approval from local ethics committees of the participating hospitals. After informed consent had been obtained, patients were randomly (1:1) allocated to UAE or hysterectomy.

PROCEDURES

As described earlier UAE and hysterectomy were performed according to protocol and professional standards. See table 1 for type of hysterectomy and UAE [8;9].

TABLE 1. Baseline and procedural characteristics

	UAE N=88 N (%)	Hysterectomy N=89 N (%)
Age (years)		
Mean (SD)	44.6 (4.8)	45.4 (4.2)
Body Mass Index (weight (kg) / length (m)2)		
Mean (SD)	26.7 (5.6)	25.4 (4.0)
Parity		
0	30 (34.1)	20 (22.5)
>1	58 (65.9)	69 (77.5)
Ethnicity		
Black	24 (27.3)	20 (22.5)
White	54 (61.4)	57 (64.0)
Other	10 (11.4)	12 (13.5)
Marital status		
Single	16 (18.2)	13 (14.8)
Married	55 (62.5)	54 (61.4)
Living Apart Together	5 (5.7)	4 (4.5)
Divorced	12 (13.6)	15 (17.0)
Widow	0 (0)	2 (2.3)
Employment status		
Employed	68 (77.3)	69 (78.4)
Unemployed	20 (22.7)	19 (21.6)
Smoking status		
Current smoker	21 (23.9)	23 (25.8)
Former smoker	11 (12.5)	14 (15.7)
Non-smoker	56 (63.6)	52 (58.4)
Highest educational level		*1
Elementary school	3 (3.4)	6 (6.9)
Lower vocational, lower secondary school	29 (33.0)	32 (36.8)
intermediate and higher vocational, higher secondary school	26 (29.5)	27 (31.0)
College/University	28 (31.8)	22 (25.3)
Other	2 (2.3)	0 (0)
Previous treatment		
None	11 (12.5)	15 (16.9)
Hormonal	59 (67.0)	59 (66.3)
Non-Steroidal-Anti-Inflammatory-Drugs / **T**ranexaminacid	45 (51.1)	41 (46.1)
Iron-supplement/blood transfusion	50 (56.8)	52 (58.4)
Surgical procedures	17 (19.3)	11 (12.4)

TABLE 1. Continued

		UAE N=88 N (%)	Hysterectomy N=89 N (%)
Symptoms			
Menorrhagia		88 (100)	89 (100)
Dysmenorrhoea		47 (53.4)	50 (56.2)
Pain (not during menstruation)		15 (17.0)	14 (15.7)
Anemia		43 (48.9)	42 (47.2)
Pressure symptoms		23 (26.1)	25 (28.1)
Other symptoms		6 (6.8)	11 (12.4)
Duration of symptoms (months)			
Median (range)		24 (3-250)	24 (4-240)
Number of fibroids			
Median (range)		2 (1-20)	2 (1-9)
Uterine volume (cm3)			
Median (range)		321 (31-3005)	313 (58-3617)
Fibroid volume (dominant fibroid, cm3)			
Median (range)		59 (1-673)	87 (4-1641)
Type of UAE			
Target embolization	Left uterine artery	65	-
	Right uterine artery	59	-
Selective embolization	Left uterine artery	8	-
	Right uterine artery	12	-
Type of hysterectomy		(N=4)	
Abdominal hysterectomy		2	63
Vaginal hysterectomy		1	8
Vaginal hysterectomy with mercellation		1	1
LH with mercellation		-	2
LAVH		-	1

SAMPLE SIZE AND ENDPOINTS OF THE STUDY

The primary endpoint of the 2-year EMMY trial was elimination of heavy/abnormal menstrual bleeding in at least 75% of patients who were therefore spared a hysterectomy [8]. To reject the null hypothesis that UAE and hysterectomy are not clinically equivalent, at least 2 x 60 (= 120) analyzable patients had to be included. Endpoints after 10 years were reinterventions, quality of life, urinary and defecation function, menopausal symptoms, menstrual characteristics, and satisfaction with the received treatment.

STUDY MEASURES

During the first 2-year follow-up patients received a total of six questionnaires. After 5 and 10-years, an additional questionnaire was sent to all participants of the trial. The 10-year questionnaire was mailed when the last included patient had reached 10 years of follow-up. As a result, the questionnaire was returned after a median of 11 years of follow-up (133 months; SD 8.58). Non-responders were contacted by telephone. All questionnaires were similar except for the 5 and 10 year follow-up questionnaires, which were condensed versions of the original 6 questionnaires to optimize the response rate. The 10 year questionnaire evaluated the following subjects: additional interventions between 5- and 10-years of follow-up, HRQOL, urinary and defecation function, menopausal symptoms, menstrual characteristics (bleeding symptoms since UAE or no symptoms due to successful UAE or menopause) and satisfaction.

Generic HRQOL

Health status and HRQOL was evaluated using the Medical Outcome Study Short Form (SF)-36 [17;18]. The SF-36 generates 2 summary scores: The physical component summary (PCS) and the mental component summary (MCS) [19] The scores range from 0-100 and were validated for the Dutch population. Higher scores represent better physical or mental functioning.

Urinary function and defecation

Urinary and defecation functioning was evaluated using the validated urogenital distress inventory (UDI) and the defecation distress inventory (DDI) [20-22]. The UDI was used to investigate urinary symptoms. The UDI score ranges from 1-100. Higher scores represent worse functioning. The same applies to the DDI, which was used to score defecation symptoms. Patients were asked to rate the overall quality of urinary and stool function: very good, good, not good, nor bad, fairly bad, bad, or very bad. Furthermore, an inquiry was made if patients used pads for urinary incontinence or laxatives.

Menopause

Menopausal symptoms were evaluated by the Kupperman score as modified by Wiklund et al [23] Scores range from 0-51, where higher scores represent more serious menopausal symptoms.

Satisfaction

We inquired whether the patients would recommend the primary treatment to a friend and whether or not they would indeed have chosen the assigned treatment again if they would have the opportunity to do so. Finally, patients were asked to indicate how satisfied they were with the received treatment on a 7-point Likert scale: very satisfied, satisfied, fairly satisfied, not satisfied/not unsatisfied, fairly unsatisfied, unsatisfied, or very unsatisfied.

Statistical analysis

Statistical software (SPSS, Version 20.0; IBM Corp, Armonk, NY) was used for analyses. Study outcomes were analyzed according to original treatment assignment (intention to treat). Comparison of differences in categorical data was assessed with the c2 test (or Fisher exact test, if appropriate). Differences in numeric data were assessed by the unpaired Student t test. Predictors for secondary hysterectomy were analyzed by binary logistic regression. Whenever univariate analyses within baseline characteristics (Appendix) yielded a P value <.1 these were included for binary logistic regression. Differences in HRQOL between the groups were assessed with the unpaired Student t tests. Repeated measurement analysis was used to evaluate longitudinal differences (MCS, PCS, UDI, DDI, and Wiklund scores) between the treatment strategies with time as a repeated factor (covariance structure: unstructured). Multiple linear regression analyses were performed for baseline characteristics (Appendix) that yielded P values <.1 in univariate analyses to evaluate the impact of these characteristics on the MCS, PCS, UDI, and DDI change scores at 10 years compared to baseline. P<0.05 (2-sided) was considered statistically significant in all analyses.

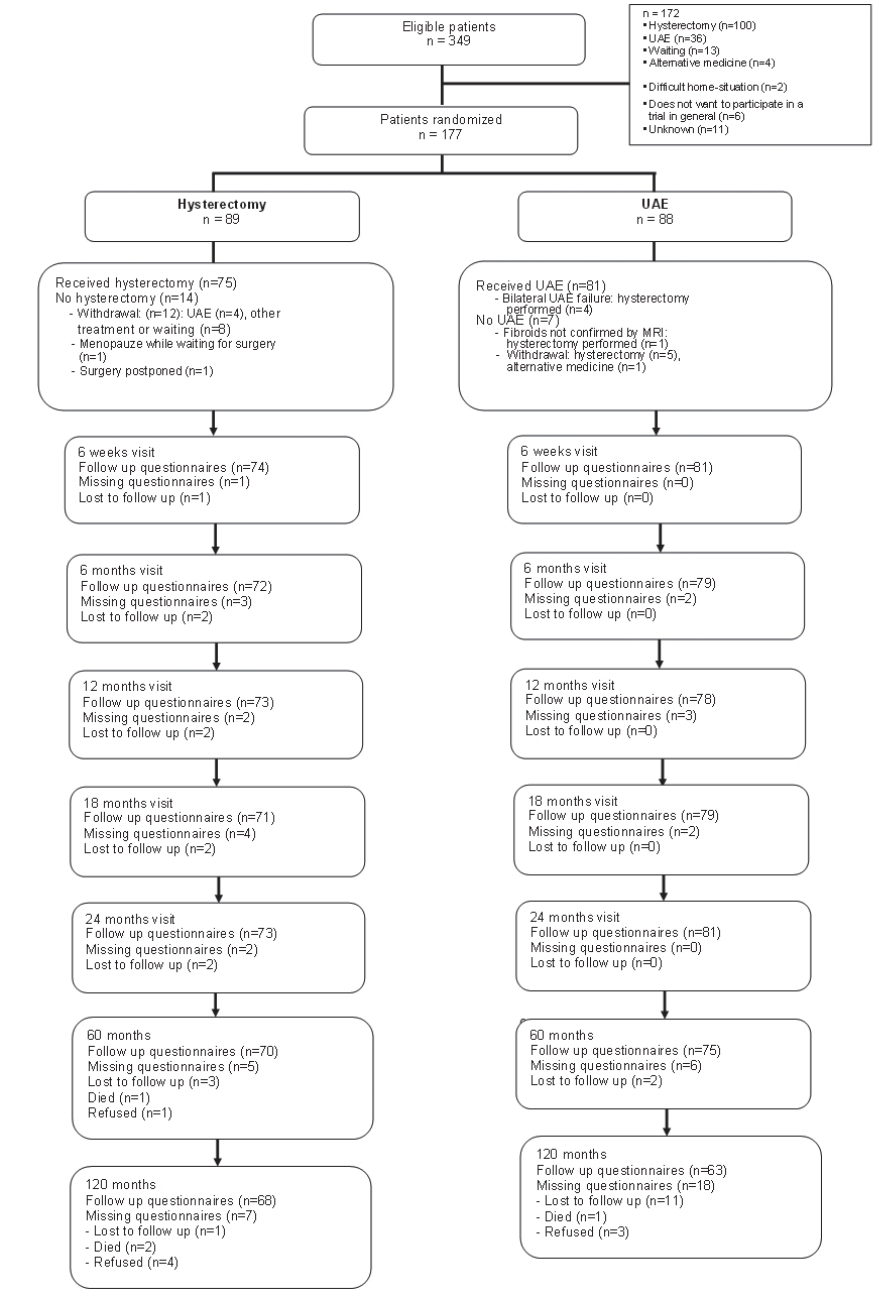
RESULTS

PATIENTS

Enrollment took place from March 2002 through February 2004 in 28 of 34 hospitals in The Netherlands. A total of 75 women vs 81 women received hysterectomy or UAE, respectively. Baseline and procedural characteristics are listed in Table 1. The patient flow is described in Figure 1; 84% of the mailed 10-year questionnaires were returned, with a mean follow-up of 133 months (SD 8.58 for analytical purposes, the median time of 11 years is depicted as a fixed point in time and mentioned hereafter as “10 years”). The remaining 16% consisted of nonresponders due to emigration (n = 3), unknown address (n = 10), refusal to participate (n = 9), or death (n = 3).Of the nonresponders 10 patients underwent

UAE without secondary hysterectomy. The median age of all patients responding to the 10-year questionnaire was 56 years (range 45-68).

FIGURE 1. Patients flow through trial and follow-up period



CLINICAL OUTCOME ALREADY REPORTED

In the first 2 years of follow-up, 19 secondary hysterectomies were performed (23.5%): 4 because of bilateral UAE failure and another 15 because of clinical failure during follow-up [8]. At 2-5 years an additional 4 secondary hysterectomies were performed, because of insufficient improvement of menstrual bleeding symptoms, thus increasing the total secondary hysterectomy rate after 5 years to 28.4% [6].

CLINICAL OUTCOME AT 10 YEARS

In addition to these 23 secondary hysterectomies, another 5 hysterectomies were required between 5-10 years (Figure 2). This totals 28 (35%) secondary hysterectomies after 10 years. Secondary hysterectomies were performed because of persistent menstrual problems or pain in all cases but 1, which was carried out for prolapse. Per protocol analysis showed that 24 of 77 (31%) patients underwent a secondary hysterectomy after a technically successful UAE, while another 4 patients in the UAE group had a bilateral embolization failure and subsequently had a hysterectomy. Three of the patients who underwent unilateral embolization (30%) had a secondary hysterectomy, all within the first 2 years of follow-up. A total of 10 of 81 (12%) patients underwent unilateral embolization. Of these 10 patients, 3 of 28 (10.7%received a secondary hysterectomy) and 8 of 53 (13.2%) did not. UAE failure within 10 years of follow-up was associated with a body mass index >25 (odds ratio, 3.29; 95% confidence interval [CI], 1.14-9.55; P = .028) and smoking (odds ratio, 3.24; 95% CI, 1.08-9.68; P = .036) in the multivariate analysis. An overview of all additional interventions performed within 10 years in the UAE group and hysterectomy group are listed in Table 2.

FIGURE 2. Kaplan-Meier curve for preservation of the uterus after UAE

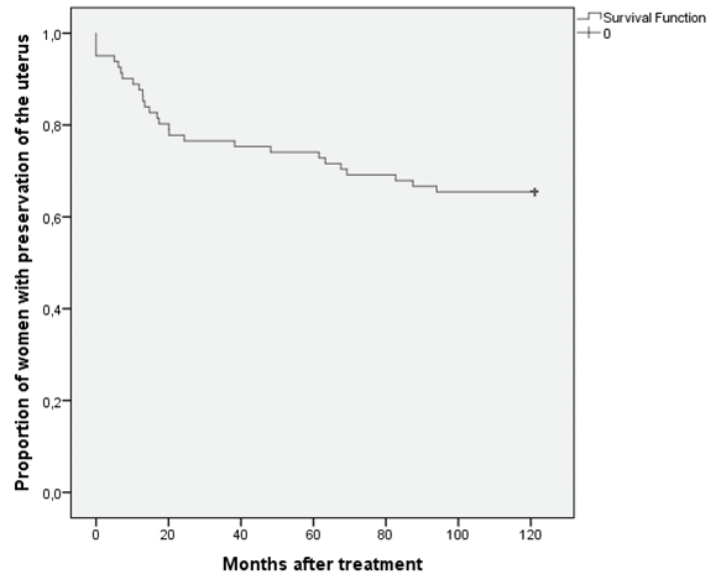


TABLE 2: Reinterventions in UAE and hysterectomy group through 10 years after initial treatment

Primary intervention	Secondary intervention	Reason for intervention	Time since primary intervention (mnths)
UAE			**Until 2 years**
1	Abdominal hysterectomy	Bilateral failure UAE	<1
2	Abdominal hysterectomy	Bilateral failure UAE	<1
3	Abdominal hysterectomy	Bilateral failure UAE	<1
4	Vaginal hysterectomy with morcellation	Bilateral failure UAE	<1
5-1	Failed attempt to hysteroscopically remove myoma under general anesthesia	Persistent abdominal pain/ myoma nascens	1

TABLE 2. Continued

Primary intervention	Seconday intervention	Reason for intervention	Time since primary intervention (mnths)
UAE			**Until 2 years**
5-2	Attempt to hysteroscopic myomaresection:converted to vaginal hysterectomy	Return menorrhagia	20
6	Manual resection myoma under general anesthesia	Discharge, fever and abdominal pain/myoma nascens	2
7	Abdominal hysterectomy	Menorrhagia and persistent abdominal pain	5
8	Abdominal hysterectomy	Menorrhagia	6
9	Abdominal hysterectomy	Menorrhagia, persistent pain, bulk complaints	7
10	Abdominal hysterectomy	Menorrhagia	7
11	Abdominal hysterectomy	Persistent abdominal pain and irregular menstruation	10
12	Vaginal hysterectomy	Menorrhagia, persistent pain and dyspareunia	12
13-1	Diagnostic hysteroscopy with curretage	Post menstrual blood loss	12
13-2	Abdominal hysterectomy	Irregular cycle, pain and bulk complaints	13
14	Abdominal hysterectomy	Menorrhagia and bulk complaints	13
15	Abdominal hysterectomy	Return menorrhagia	13
16	Laparoscopic assisted vaginal hysterectomy	Menorrhagia	15
17	Abdominal hysterectomy	Menorrhagia	17
18	Vaginal hysterectomy	Menorrhagia	17
19	Abdominal hysterectomy	Menorrhagia	20
20	Abdominal hysterectomy	Menorrhagia	24

TABLE 2. Continued

Primary intervention	Secondary intervention	Reason for intervention	Time since primary intervention (mnths)
UAE			**Until 5 years**
21	Myomectomy	Menorrhagia	25
22	Abdominal hysterectomy	Menorrhagia	36
23	Curettage	Menorrhagia	37
24	Abdominal hysterectomy	Menorrhagia	44
25	Endometrium ablatio Novasure	Menorrhagia	47
26	Polypectomy	Menorrhagia	48
27	Abdonminal hysterectomy	Menorrhagia	48
28	Abdominal hysterectomy	Menorrhagia	63
			Until 10 years
29	Hysterectomy	Menorrhagia	64
31	Hysterectomy	Menorraghia	68
32	Hysterectomy	Menorraghia	79
33	Hysterectomy	Prolapse	93
Hysterectomy			**Until 2 years**
1-1	Adhesiolysis via laparotomy	Persistent abdominal pain	4
1-2	Bilateral adnextirpation	Persistent abdominal pain	11
2	Fistula repair using Latzko technique	Vesico-vaginal fistula	7
3	Reconstruction surgery	Incisional hernia	9
4	Adhesiolysis and cystectomy via laparotomy	Persistent abdominal pain	23
5	Diagnostic laparoscopy	Persistent abdominal pain	24

TABLE 2. Continued

Primary intervention	Secondary intervention	Reason for intervention	Time since primary intervention (mnths)
UAE			**Until 5 years**
7	Ovariectomy	Persistent abdominal pain	38
8	Sub-urethral sling procedure	Stress incontinence	50
9	Reconstruction surgery	Cosmetical	54
			Until 10 years
10	Sub-urethral sling procedure	Prolapse	64
11	Sub-urethral sling procedure	Prolapse	100
12	Sub-urethral sling procedure	Prolapse	unknown

QUALITY OF LIFE OUTCOME

HRQOL already reported

As described before, a significant improvement in general HRQOL (SF-36 MCS and PCS) occurred during the first 6 months after treatment for both groups [6;8;9]. Thereafter the scores stabilized and remained comparable between the groups during the first 5 years of follow-up. Also, the UDI score showed significant improvement in both the hysterectomy and UAE groups during the first 6 months. Hereafter, UDI scores stabilized from 6 months to 5 years in both groups at a significantly higher level compared to baseline values before treatment without significant differences between groups [9]. For defecation functioning a significant improvement was found in the UAE group between 6 months and 5 years compared to baseline. In the hysterectomy group, this was not the case. Between the groups there was no significant difference.

Generic HRQOL at 10 years

At 10 years both groups had improved significantly compared to baseline (MCS and PCS; P value <0.001) with no differences between groups. Between 5-10 years of follow-up no differences for PCS and MCS change scores between the groups were found. Table 3 shows the differences in PCS and MCS between and within groups over time. Repeated measurements analyses of the 10-year

follow-up general HRQOL scores remained stable, without differences between both groups (PCS: P = .77; MCS: P = .95) (Figure 3, A and B). Multivariate analyses of baseline variables showed a high or intermediate educational level (b, 3.02; 95% CI, 1.14-4.91; P = .002) and previous surgical treatment (b, 5.89; 95% CI, 2.25-9.53; P = .002) to be associated with improvement in PCS scores after 10 years. The increase in MCS scores after 10 years was positively influenced by a higher number of fibroids at baseline (b, 4.96; 95% CI, 0.53-9.38; P = .028).

Urinary and defecation function at 10 years

At 10 years both groups remained stable without differences between the groups (UAE: P = .93; hysterectomy: P = .59) (Table 3). Similarly, repeated measurements analyses showed no differences in UDI scores between the groups during 10 years of follow-up (P = .308) (Figure 3, C). Improvement in urinary functioning after 10 years of follow-up was associated with 1 baseline characteristic: a lower number of fibroids (b, -22.02; CI, -37.67 to -6.36; P = .007). Figure 3, D, depicts defecation function (DDI). The significant improvement of DDI scores in the UAE group was no longer present when the 10-year scores were added to the repeated measurement analysis (P = .253). Table 3 shows the differences in DDI change score between and within groups over time. Table 3 illustrates that no systematic differences for DDI change scores were present between the groups from 5-10 years of follow-up (UAE: P = .23; hysterectomy: P = .31). Multivariate analysis showed none of the baseline characteristics to be associated with improvement of defecation functioning. Urinary incontinence was present at baseline in 18.5% of UAE patients vs 14.7% of hysterectomy patients (P = .52). After 10 years 26.9% of UAE group patients reported urine incontinence compared to 29.4% of patients in the hysterectomy group (P = .76).

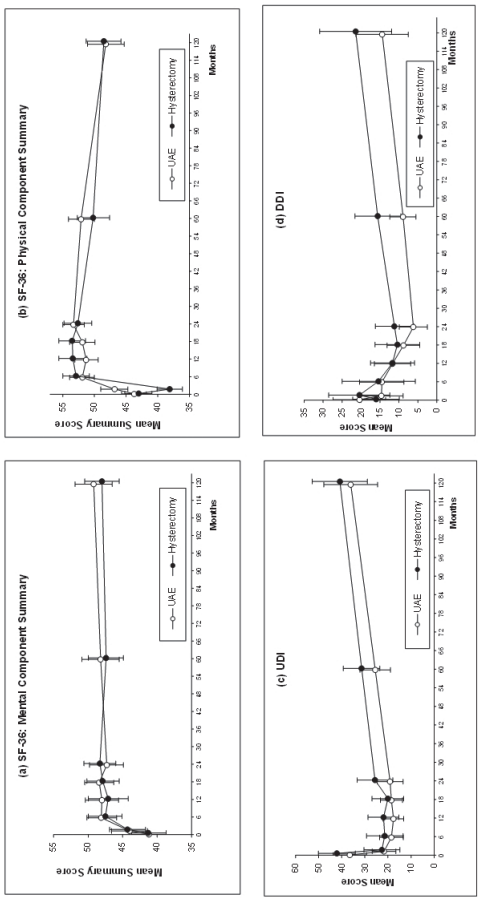
TABLE 3. Quality of life change scores through 10 years after uterine artery embolization and hysterectomy.

	12 months change score				24 months change score				60 months change score				120 months change score			
	UAE (N=81)	**Hyst. (N=75)**	**Change score difference (95%CI)**	***P* value**	**UAE (N=81)**	**Hyst. (N=75)**	**Change score difference (95%CI)**	***P* value**	**UAE (N=81)**	**Hyst. (N=75)**	**Change score difference (95%CI)**	***P* value**	**UAE (N=81)**	**Hyst. (N=75)**	**Change score difference (95%CI)**	**P value**
MOS SF-36 MCS	6.33[a]	7.67[a]	1.34 (-2.63 to 5.32)	0.505	5.80[a]	7.26[a]	1.47 (-2.78 to 5.71)	0.496	6.31[a]	6.87[a]	-0.56 (-5.07 to 3.95)	0.806	4.41[a]	4,54[a]	0.13 (-4.08 to 3.82)	0.947
MOS SF-36 PCS	7.32[a]	10.13[a]	2.81 (-0.59 to 6.21)	0.104	9.42[a]	9.32[a]	-0.096 (-2.98 to 2.79)	0.948	8.47[a]	7.20[a]	1.26 (-2.16 to 4.70)	0.468	7.31[a]	7.04[a]	0.26 (-3.93 to 4.46)	0.900
UDI	-17.16[a]	-17.88[a]	-0.72 (-9.74 to 8.30)	0.875	-17.03[a]	-14.66[a]	2.37 (-8.13 to 12.87)	0.656	-10.70[a]	-8.41[a]	-2.29 (-13.45 to 8.87)	0.686	-0.42	3.17	-3.59 (-18.65 to 11.46)	0.638
DDI	-5.90[a]	-4.99	0.91 (-6.55 to 8.36)	0.810	-14.42[a]	-5.39	9.03 (-0.82 to 18.88)	0.072	-12.72[a]	0.01	-12.73 (-22.31 to -3.15)	0.010[a]	-5.03	5.16	-10.18 (-23.11 to 2.75)	0.122

*note: CI, confidence interval, DDI, defecation distress inventory; MCS, mental component summary; MOS, Medical Outcome Study; PCS, physical component summary; SF, Short Form; UAE, uterine artery embolization; UDI, urogenital distress inventory.

[a] *Indicates a statistically significant (P .05) change from baseline in the within group analysis*

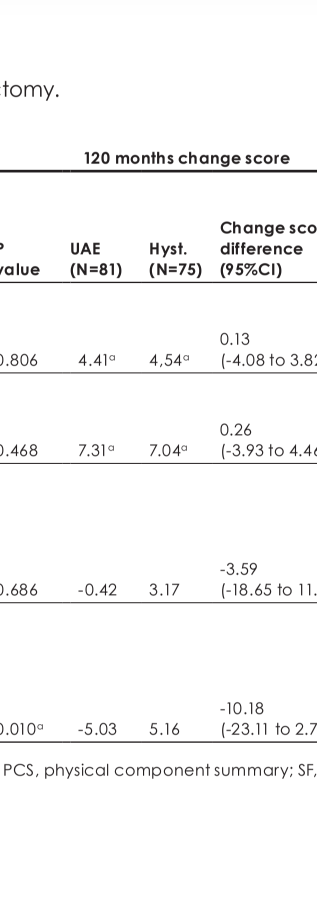
FIGURE 3. Graphs show health related quality of life scores through 10 years of follow-up



Menopause

The 10-year questionnaire contained the question: "do you feel that you are in or beyond menopause?" In all, 26 of 62 (42%) patients in the UAE group and 29 of 67 (43%) in the hysterectomy group answered "yes" (P = .88). Figure 4 shows the mean Wiklund score over time. Within-group analyses showed a significant increase in menopausal symptoms score in the hysterectomy group (+5.06; 95% CI, 2.01-8.11; P = .002) and UAE group (+3.28; 95% CI, 0.68-5.87; P = .014) from baseline compared to 10 years later. Repeated measurements analyses revealed no differences between UAE and hysterectomy after 10 years.

FIGURE 4. Wiklund score for menopausal symptoms through 10 years of follow-up



Menstrual/bleeding characteristics

Of the 53 women who had their uterus at 10 years of follow-up, 7 (13%) still reported menstrual blood loss, however only 3 reported a lot to a fair amount, 2 women reported very little to none, and 2 women reported not being sure about menstrual blood loss. Among women who underwent a primary hysterectomy or a secondary hysterectomy after an initial UAE, 5 of 103 (5%) reported occasional vaginal blood loss.

Satisfaction and preference

At 10 years after the intervention, the majority of patients declared being satisfied about the received treatment: 78% in the UAE group vs 87% in the hysterectomy group (P = .77) (Table 4). In the UAE group 81% (51/63) would advise a friend to undergo an embolization, while 84% (57/68) of patients in the hysterectomy group would recommend a hysterectomy to their friends (P = .48). As published earlier [14] most patients had a strong preference for their allocated treatment. This did not change over time: 74.2% (46/62) of patients from the UAE group preferred UAE, while 71.2% (47/66) women from the hysterectomy group preferred hysterectomy (P<0.71).

TABLE 4. Satisfaction through 10 years after uterine artery embolization and hysterectomy

	12 months			24 months			60 months			120 months		
	UAE (N=81)	Hyst. (N=75)	P value	UAE (N=81)	Hyst. (N=75)	P value	UAE (N81)	Hyst. (N=75)	P value	UAE (N=81)	Hyst. (N=75)	P value
Very satisfied	29	48	0.001[a]	34	45	0.020[a]	37	42	0.13	34	32	0.77
Satisfied	21	14		29	16		27	20		22	24	
Moderately satisfied	18	3		11	5		4	4		5	7	
Not satisfied nor unsatisfied	5	3		2	3		1	3		2	2	
Moderately unsatisfied	3	1		3	0		3	0		0	0	
Unsatisfied	1	1		1	1		3	1		0	2	
Very unsatisfied	1	0		0	3		0	0		0	0	

*note: UAE, uterine artery embolization.

[a] Indicates a statistically significant (P <0.05) change from baseline in the within-group analysis.

COMMENT

This 10-year follow-up study describes the long-term outcomes of a large randomized trial that compared UAE with hysterectomy. We conclude that UAE is a well-documented valuable treatment alternative for surgery in the

treatment of patients with symptomatic fibroids in terms of quality of life. This view is supported by a recent Cochrane review [24].

MOST IMPORTANT CLINICAL FINDINGS

The necessity to perform a secondary hysterectomy after a median follow-up of approximately 11 years occurred in 35% (27) of UAE patients. This results in a success rate of 69% after an initially successful UAE (excluding 4 initial technical failures of UAE). The continuous increase of women undergoing hysterectomy beyond a follow-up of 5 years underlines the importance of studying long-term outcomes. A longer follow-up provides important insights for counselling patients and prediction of quality of life. This article reports the longest follow-up so far from a randomized comparison between UAE and hysterectomy. Other publications concerning shorter (≤5 years) follow-up time frames show higher success rates [5;25]. Lower success rates, as reported in our study, may be explained by: (1) our initial selection criteria, where we selected the worst group of patients with no option other than a hysterectomy; (2) the fact that reembolizations were not performed in the study, which also may have resulted in higher hysterectomy rates; (3) the multicenter design of our trial: our results were not derived from a single high-volume center that, arguably, may have better UAE results; and (4) a longer follow-up than any other study in which we demonstrated that even between 5-10 years secondary hysterectomies are performed. Our finding that secondary hysterectomy within 5- 10 years of follow-up was associated with a body mass index >25 and smoking at baseline might be of importance in counselling patients. The same finding was reported between 2-5 years of follow-up [6]. The most striking increase in HRQOL in both study arms occurred in the first 6 months after treatment and remained stable for 10 years without differences between both groups [9]. However, after 5 years of follow-up a decrease in PCS scores occurred in both groups, which seems to be explained best by increasing age and (befitting) consequential physical decline. The 10-year multivariate analysis for baseline variables showed previous surgical treatment and high or intermediate educational level to be associated with improvement of PCS scores. Previous gynecological treatment as an influencing factor for PCS might be explained by patients having a worse physical condition at baseline, thus enabling a higher physical benefit from treatment. In the general population, a high or intermediate educational level is often associated with a better physical and mental condition [26]. Consequently, it is not surprising that these patients had a higher chance of increased PCS scores. Analyses also showed "no previous treatment" to be associated with lower PCS change scores, hence

the possibility that these patients have less to gain from treatment because of better PCS scores at baseline. For the first time in follow-up UDI and DDI scores showed no significant improvement compared to baseline scores, which may be explained by physical decline due to increasing age, but not influenced by keeping the uterus. Earlier we reported on a significantly better defecation function as a new finding in the UAE group, however repeated analyses of our 10-year follow-up data no longer showed this difference [6]. This might be explained by the fact that there were fewer respondents, resulting in insufficient power to remain significant (the effect size was still present but the CI widened) (Table 3). We note that there is still a trend toward better defecation function in the UAE group compared with the hysterectomy group (Figure 3, C and D). Menopausal symptoms did not reveal any differences between both treatment arms. It did however find a significant increase in Wiklund scores over time in comparison to baseline values in both groups, probably explained by more women reaching (perimenopausal) menopausal age. The mean age for reaching menopause in industrialized societies is 51 years [27;28], while the mean age of women in the embolization and hysterectomy groups was 55 and 56 years, respectively. Only 7 women in the UAE group still reported menstrual blood loss. Three of these are theoretical candidates for hysterectomies in the future since they value the amount of blood loss as more than a normal menstruation.

STRENGTHS AND LIMITATIONS OF THIS STUDY

Our study is the only randomized controlled trial ever published with 10 years of follow-up results and therefore important in providing clinicians with unique insight for patient counselling in terms of clinical outcomes and various aspects of quality of life. However, our response rate was not 100%, which might contribute to insufficient power for reaching significant results. Ten patients in the UAE group did not have a secondary hysterectomy at 5-year follow-up and did not respond to the 10-year questionnaire, however we find it very unlikely that all of these patients underwent hysterectomy between 5-10 years of follow-up. Furthermore, surgical techniques for both hysterectomy and UAE have changed over the years; currently, hysterectomies are progressively done by laparoscopy and technical failures for UAE are becoming less prevalent. This might have influenced results, when the study would have been performed currently.

CONCLUSION

After 10 years of follow-up, in 69% of all women undergoing a technical successful UAE, a hysterectomy was avoided. Also, HRQOL and satisfaction rates did not differ between the randomized groups. In view of the short- and long-term available clinical and quality-of-life evidence, we conclude that all women who are candidates for hysterectomy because of symptomatic uterine fibroids should be counseled on the option of UAE.

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SUPPLEMENTARY MATERIALS

APPENDIX. Baseline characteristics

Predictors for failure	Effect of baseline-variables on HRQOL
Age (continuous)	idem
Ethnicity (Caucasian as reference category)	idem
BMI (continuous)	idem
Parous (yes/no)	idem
Smoking (yes/no)	idem
educational level (intermediate level -or higher- versus lower level)	idem
Married (yes/no)	idem
Paid work (yes/no)	idem
Co-morbidity (yes/no)	idem
Previous surgical treatment (yes/no)	idem
Previous hormonal treatment (yes/no)	Any previous treatment (yes/no)
Duration of menorrhagia symptoms (>/< 1 years)	duration of menorrhagia symptoms (continuously)
Hemoglobine level (continuous)	previous iron-substitution therapy/blood transfusion (yes/no)
Anemia (yes/no)	Anemia before treatment (yes/no)
Number of fibroids (continuous)	idem
Uterine volume (continuous)	idem
Volume of fibroids (continuous)	idem
	intended treatment (UAE/hysterectomy)
	baseline and after 24 months SF-36 MCS (continuously, not on MCS change outcome)
	Baseline and after 24months SF-36 PCS (continuously, not on PCS change outcome).

3

Implementation of uterine artery embolization for symptomatic fibroids in the Netherlands: an inventory and preference study

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ABSTRACT

BACKGROUND AND PURPOSE

The Dutch national guideline on heavy menstrual bleeding was updated and published in 2013. It recommended (for the first time) that uterine artery embolization (UAE) should be part of counseling of women with symptomatic fibroids. We aimed to evaluate the implementation of UAE for symptomatic uterine fibroids in the Netherlands and to investigate gynecologists preference and other influential factors.

METHODS

The primary outcome was to examine the UAE/hysterectomy ratio before and after introduction of the 2013 guideline by the use of annual hospital reports. The secondary outcome assessed factors that could influence implementation by means of a questionnaire to gynecologists.

RESULTS

A total of 29/30 (97%) UAE+ hospitals and 36/52 (69%) UAE- hospitals sent their annual reports. The UAE/hysterectomy ratio in 2012, 2013 and 2014 were 7,0 %, 7.0% and 6.9%, respectively. Regarding the questionnaire, the response rates were 88% and 91%, respectively. In both groups we observed a high self-perceived tendency for UAE counseling (90% versus 70%, p= 0.001). Approximately 50% of gynecologists from UAE- hospitals indicate they have insufficient information about UAE for appropriate counseling and 40% doubts the effectiveness of UAE. Furthermore, in the majority of gynecologists some 'urban myths' about the effectiveness and side-effects of UAE seem to persevere.

CONCLUSION

Adding UAE as a treatment option to the national guideline did not change the number of performed UAEs for symptomatic fibroids. It might be useful to develop an option grid in order to offer appropriate, independent counseling and encourage shared decision making.

INTRODUCTION.

Approximately 10-30% of fertile women suffer from heavy menstrual bleeding [1]. In 40% of these women uterine fibroids are present [2]. In the last few years multiple randomized controlled trials and a Cochrane review have been conducted and demonstrated UAE to be a valid and safe alternative for hysterectomy in patients with symptomatic uterine fibroids [3-9]. Long-term follow-up showed comparable Health-Related Quality of Life (HRQOL) and treatment satisfaction rates after 5 and 10 years of follow-up [5, 6]. Also, UAE is less expensive than hysterectomy [5, 10]. Despite these results, UAE seems to be offered infrequently and implementation seems slow [11]. A pilot study published in 2011 showed the lack of a guideline in the management of heavy menstrual bleeding to be the main cause of infrequent UAE in the Netherlands [12]. In response to this finding, a national guideline for gynecologists was published in 2013. Regarding UAE, this guideline specifically recommends informing the patient of the following outcomes 5 years after the initial treatment (UAE versus hysterectomy); 1) an improved quality of life comparable to that of patients who underwent hysterectomy, 2) faster recovery and return to work after UAE compared to hysterectomy, 3) in 75% of patients who underwent successful UAE no hysterectomy was needed [13].

Most hospitals in the Netherlands are non-profit foundations, whereas most healthcare insurers are for-profit organizations [14]. In general, there are three types of hospitals; 1) university hospitals, 2) teaching hospitals and 3) general hospitals. University hospitals are academic medical centers connected to the medicine faculty of a major university. These university hospitals provide the most complex and specialized healthcare. The teaching hospitals work together with university hospitals (training of nurses, medical interns and residents) and offer a greater variety of specialisms and treatment options compared to general hospitals. General hospitals provide standard healthcare for less specialized problems and refer, if necessary, to more specialized hospitals [15]. UAE is considered specialized care. It is executed by interventional radiologists and is offered in all academic hospitals, most teaching hospitals and some general hospitals. Insurance companies allow patients to choose where they want to be treated and with the exception of an obligatory deductible excess, all specialized healthcare costs are covered by the insurer. In these different hospitals standard practice for counseling for UAE differs. Some gynecologists working in UAE+ hospitals include the interventional radiologists in the counseling process, whereas others counsel patients themselves. There is no national guideline of protocol for UAE specifically. The aim of this study was 1) to examine the UAE/hysterectomy ratios before and after introduction of the 2013 Dutch national gynecological guideline for heavy

menstrual bleeding, 2) to evaluate the different aspects of UAE counseling, preference, difficulties, knowledge/awareness and suggestions to improve implementation by the use of a questionnaire survey among gynecologists working in UAE+ and UAE- hospitals.

MATERIALS AND METHODS

STUDY DESIGN

This is a group comparison design study, which consists of two steps to answer our research questions: 1) Was there an increase in UAEs after the new introduced guideline in 2013? How did this effect the UAE/hysterectomy ratio? 2) Is there a difference in counseling and preference between gynecologists working in a UAE+ hospital versus a UAE- hospital?

Our primary outcome consisted of UAE/hysterectomy ratios in 2012 compared to 2014 in order to evaluate UAE implementation of the 2013 national guideline. Our secondary outcome assessed the different aspects of UAE counseling, preference, difficulties and knowledge/awareness by the use of a questionnaire survey among gynecologists working in UAE+ and UAE- hospitals.

We hypothesized that the incidence of UAE counseling and quality of counseling was comparable between UAE performing and non-UAE performing hospitals. This study was approved by the Ethics Committee of the coordinating hospital.

DATA COLLECTION

We contacted and asked all 82 Dutch UAE performing and non-UAE performing hospitals to send their annual reports for the extraction of performed hysterectomy numbers. Information about the number of UAEs performed in the consecutive years 2012, 2013 and 2014 were requested from the interventional radiology department.

The questionnaires were sent to selected gynecologists working at hospitals from which we received the annual data and who were identified to be performing hysterectomies themselves. The questionnaire was web based and the link was emailed to the participating gynecologists. In the questionnaire various determinants were examined concerning UAE preferences, counseling content, imaging, implementation and possible improvement suggestions for implementation (appendix 1).

DATA ANALYSIS

Statistical analyses were performed using SPSS statistical software (version 20.0). Results were presented using descriptive statistics such as frequencies, mean (± standard deviation) and median (with interquartile range) as appropriate. In normally distributed and not normally distributed data, respectively the independent T-test and the Mann-Whitney U test were used. In case of categorical data a Chi-square test/Fisher's exact test was used. P-values <.05 were considered statistically significant.

RESULTS

We received the annual hospital year reports over 2012, 2013 and 2014 of 29/30 (91%) UAE performing and 36/52 (69%) non-UAE performing hospitals. Hysterectomies were documented by detailed operation mode, as mentioned in the annual report. No specific information or ICD-10 codes concerning the indication of the hysterectomy were available. Hysterectomies with vaginoplasty and radical hysterectomies were excluded.

Out of the 30 UAE+ hospitals, we received numbers of performed UAEs from 29/30 radiology departments (91%). The calculated UAE/hysterectomy ratios showed UAE percentages of (9/(120+9)) 7,0%, (9/(120+9)) 7.0% and (8/(108+8)) 6.9% in 2012, 2013 and 2014, respectively. Table 1 outlines the total amount of UAE, hysterectomies in UAE+ hospitals and UAE ratios .

TABLE 1. Mean number of UAE's, hysterectomies per UAE+ hospital (n=29) and UAE/hysterectomy ratio.

Year	UAE (SD, range)	Hysterectomies UAE+ hospitals n=29 (SD, range)	UAE/hysterectomies performed in UAE+ hospitals (%)
2012	9 (19.1; 0 – 100)	120 (44; 26 - 212)	7.0
2013	9 (19.1; 0 – 99)	120 (39; 27 - 204)	7.0
2014	8 (17.1; 0 – 91)	108 (51; 0-209)	6.9

When sending the 2017 questionnaires to the hospitals that responded with their annual data, it became apparent that some hospitals started or stopped UAE. The questionnaires were filled in by 43 gynecologists working at UAE+ and 43 gynecologists from UAE- hospitals, resulting in a comparable hospital response rate of 88% (28/32) and 91% (30/33) respectively.

COUNSELING AND CONTRA-INDICATIONS FOR UAE

Gynecologists working at UAE + hospitals estimated to counsel as often (scale 0-10, with 0 meaning ''I never counsel" and 10 "I always counsel": median=9; IQR 6-10) as gynecologists working at UAE- hospitals (median 7; IQR 3-8), (p=0.001). Moreover, gynecologists from UAE+ hospitals estimated to counsel a median of 20 patients per year (IQR 1-40), whereas gynecologists in UAE- hospitals counseled a median of 10 patients per year (IQR 1-20) (p=0.021).
Gynecologists were asked to rate contraindications to UAE. Table 2 outlines the differences concerning these ratings between the gynecologists working at UAE- and UAE+ hospitals. None of the ratings were statistically significant different between groups and both groups considered type 7 subserous pedunculated fibroids and a wish to conceive a contraindication (>5 on a scale of 0-10).

TABLE 2. Possible contraindications to UAE

Contraindication (Median, IQR)	UAE+ (n=43) (median, IQR)	UAE- (n=43) (median, IQR)	P-value
Subserous pedunculated fibroid (type 7)	7.00 (5-9)	7.00 (5-9)	0.07
Submucous fibroid (type 2)	2.00 (0-5)	1.00 (0-3)	0.68
Only bulky complaints	3.00 (1-7)	3.00 (1-7)	0.71
Suspected concurrent adenomyosis	4.00 (1-7)	5.00 (2-7)	0.15
Uterus size > 20 weeks of gestation	4.00 (2-6)	5.00 (3-8)	0.49
A wish to conceive	9.00 (8-10)	8.00 (8-10)	0.16

*note: Median on a scale of 0-10; 0=no, it is no contraindication for UAE 10= yes, I it is a contraindication for UAE. IQR = Interquartile range P-value calculated with Mann-Whitney U test.

COUNSELING BY THE INTERVENTIONAL RADIOLOGIST (IR)

Gynecologists working at UAE+ hospitals were asked if the IR is involved in the counseling process. In 18/28 (64%) of UAE+ hospitals the IR is involved. In the remaining 10 UAE+ hospitals the IR is not involved in the counseling process, however 8/14 (57%) of gynecologists working at these hospitals answered this should be standard practice.
In UAE- hospitals 11/43 (26%) of gynecologists stated the IR should not be involved in the counseling process, 12/43 (28%) answered "only if it is preference of the patient" and 16/43 (37%) answered "the interventional radiologist should always be involved".

PERFORMING HYSTERECTOMIES

Almost all (98%) of gynecologist working in UAE+ and UAE- hospital answered they perform hysterectomies. 36/42 (86%) of the gynecologists working at the UAE+ hospitals answered they perform hysterectomies <50 times a year compared to 31/41 (75%) of the gynecologists at UAE- hospitals. The remaining gynecologists answered they perform 50-100 hysterectomies a year.

CHANGES AFTER THE 2013 GUIDELINE AND UAE IMPLEMENTATION

Gynecologists answered that UAE is offered more often 16/43 (37%) in UAE+ hospitals versus 19/43 (44%) in UAE- hospitals. In both groups, about half of the group replied nothing changed after the introduced guideline in 2013.Table 3 displays the most interesting distribution of answers to a variety of implementation and counseling questions between the two groups.

TABLE 3. Questions asked in the survey for both gynecologists working at UAE+ and UAE- hospitals

Questionnaire statements	Gynecologists in UAE+ hospitals (%)	Gynecologists in UAE- hospitals (%)	P-value
Implementation	Answered yes	Answered yes	
Everybody with fibroids should be counseled for UAE.	98% (42/43)	88% (38/43)	0.20+
I have doubts about the effectiveness of UAE.	0% (0/43)	40% (17/43)	0.00*
I do not wish to transfer care to another specialist.	0% (0/43)	20% (9/43)	0.00+
Counseling	Confirmed statement	Confirmed statement	
1.UAE causes more pain than other treatments.	51% (20/39)	74% (28/38)	0.04*
2. UAE patients recover faster than hysterectomy patients and resume work faster. (true)	82% (32/39)	63% (24/38)	0.06*
3. After a successful UAE, there is a 50% chance of secondary hysterectomy. (false)	46% (18/39)	87% (33/38)	0.00*
Counseling problems and difficulties	Confirmed statement	Confirmed statement	
Option A: The patient does not choose to undergo UAE.	51% (22/43)	51% (22/43)	1.00*
Option B: Logistics are too complicated.	21% (9/43)	NA	
Option C: I do not wish to refer my patient	NA	5% (2/43)	
Option D: It is too complicated to refer	NA	7% (3/43)	
Counseling information	Confirmed statement	Confirmed statement	
1.There is insufficient information available	23% (9/39)	47% (18/38)	0.03*
2. I have sufficient knowledge	77% (30/39)	53% (20/38)	0.03*

PAIN MANAGEMENT AND COUNSELING CONTENTS

Regarding pain management, 25/28 (89%) of UAE+ hospitals has a pain protocol containing PCA analgesia in 70% and EDA in 53%.

As displayed in table 3, the statement "after a successful UAE there is a 50% chance for hysterectomy re-intervention" (p=0.000) was statistically significant different, between the UAE+ and UAE- hospitals. This statement is false.

Another statistically significant difference (p=0.03) was observed in favor of UAE+ hospitals concerning knowledge about UAE and counseling. Approximately half of gynecologists working at UAE- hospitals answered they have insufficient

information and knowledge for appropriate counseling and 40% of gynecologists in UAE- hospitals doubt the effectiveness of UAE (p=0.00).

IMPROVEMENT OF AVAILABLE INFORMATION

Recommendations regarding improvement of UAE counseling was answered as follows: 1) there should be a nationally general patient information leaflet, 2) there should be a national conference day or course day every year and 3) there should be an UAE guideline for gynecologists published on the website of the national association of gynecologists".
Also, an option grid was mentioned.

DISCUSSION

MAIN FINDINGS

Despite adding the recommendation to counsel on UAE for symptomatic fibroids to the national guideline on heavy menstrual bleeding, no increment in UAE was observed.
It appears that gynecologists working at UAE+ hospitals estimate to counsel more patients for UAE compared to the their colleagues in UAE- hospitals (p=0.001). Gynecologists in UAE+ and UAE- hospitals said UAE is offered more and counseling increased after the 2013 guideline. However, in both groups, about half of the group reported no change after the introduced guideline in 2013 opposing their earlier answers.
Gynecologists from UAE+ and UAE+ hospitals showed comparable opinions concerning contra-indications for UAE and most gynecologists from both hospitals agree that the interventional radiologist should be part of the counseling process.
Implementation of UAE in the Netherlands is slow and gynecologists do not agree if asked about its origin. Concerning UAE counseling, both groups overestimate the risk of re-intervention. This was illustrated by the fact that they indicated the statement "the secondary hysterectomy rate is 50%" to be true. Literature (and also the guideline) state there is a secondary hysterectomy rate of 28% after 5 years of follow-up and 31% secondary hysterectomies after 10 years [5, 6]. Apparently this has not reached the surveyed gynecologists.

INTERPRETATIONS OF FINDINGS

It is possible that the effect of the 2013 guideline will only become apparent after 2014 since it is known that implementation into general practice may take more time [16].

About 51% of gynecologists in UAE+ hospitals versus 52% of the gynecologists in UAE- hospitals mentioned that the patient simply declines UAE when she is counseled. Assuming this is true, why does the patient decline UAE? Twijnstra et al. [17] described the discrepancy between preferences of gynecologists for different hysterectomy types owing to variation in daily practice with these types of hysterectomies. He quoted the discrepancy that some countries prevail abdominal hysterectomy as the choice for type of hysterectomy [18-20] while this is in contrast with the preference of well-counseled patients, who prefer a laparoscopic hysterectomy [21]. It is very likely, that the preference of the patient is influenced by the experience and preference of the counseling gynecologist. Good counseling should be based on facts and should be free of personal preferences of the health care professional. In the case of UAE, counseling is mostly performed by the physician that does not execute the actual procedure. This could be of major influence.

Hysterectomy and UAE are both procedures which could be very painful so a good pain regimen is absolutely necessary. With sufficient pain relief like a PCA pump, patients do have less pain after UAE [22]. Despite the working frame of the PCA pump, some patients need an alternative pain relief like Epidural Analgesia (EDA). [23] Van der Kooij et al. [24] found that EDA would be a more effective pain relief for UAE in the first 6 to 24 hours after the UAE. In this study 89% of the UAE+ hospitals said that they had a pain protocol. However, when UAE is considered too painful, there must be inadequate pain relief.

STRENGTHS AND LIMITATIONS

To our knowledge this is the first study investigating the implementation of UAE in terms of the exact number of performed hysterectomies and UAEs and the counseling process.

We included nearly all UAE+ Dutch hospitals and received a very high response rate of the hospitals and gynecologists, which gave us a valuable reflection of daily practice and thoughts and preferences in the counseling process for UAE. However, this study is not without limitations. Two hospitals had only the hysterectomies of 2012 and 2013 available and also we had no indications for the hysterectomies since we had the intention to include hysterectomies with indication uterine fibroids. As mentioned earlier, we excluded all hysterectomies with a vaginoplasty but 5 hospitals only mentioned vaginal hysterectomy, so we included these numbers. There could have been some selection bias here. The same applies for the hysterectomies with adnexectomy. We included all of these indications (abdominal hysterectomy/vaginal hysterectomy with or

without adnexectomy) and maybe there would have been some selection bias, because we did not know how many hysterectomies were done for indication uterine fibroids exactly. However, since this was the same for all inquired years, we do not expect a large bias in the ratio.

The same applies for the UAE's. Some hospitals fail to describe the indication for UAE and could not discriminate between uterine fibroids and post-partum bleeding. Besides, we observed a large range for the UAEs because 1 hospital was performing 97 UAEs as a mean in the three years, not determining for uterine fibroids or post-partum bleeding.

The answers of the gynecologists to the questions were estimates and therefore subjective and exact numbers are lacking. As already mentioned, some hospitals had more gynecologists answering the questionnaire. Nevertheless, it is a good reflection of the daily clinic, since gynecologists in one hospital think different about counseling for UAE. When answers to questions were descriptive, we included all questionnaires. When questions were descriptive, hospitals where more gynecologists answered had a greater part in the overall calculation. This could have been some selection bias, since preferences of gynecologists might cohere with the hospital they are working at. Evaluation of hysterectomy and UAE procedures in 2018 will provide a 5-year follow-up and more insight in implementation

CONCLUSION AND RECOMMENDATIONS

In conclusion, the publication of the 2013 national guideline which recommends UAE as a treatment option for patients with heavy menstrual bleeding and fibroids did not increase numbers of performed UAEs. The UAE/hysterectomy ratio in 2014 was 6.9 %, which is unacceptably low for a procedure with solid scientific level 1 evidence.

The availability of UAE influences the frequency and content of counseling in patients with symptomatic uterine fibroids. UAE+ hospitals estimate higher counseling numbers compared to the UAE- hospitals, without apparent influence on UAE numbers.

Despite mentioning facts and fiction on UAE in the national guideline, some ‘urban embolization myths' tend to persist. Forty percent of gynecologists in UAE- hospitals doubt effectiveness of UAE and nearly half of gynecologists in UAE+ hospitals overestimate the chance of a surgical intervention after UAE. Although there is no scientific evidence from other European countries, oral communications at scientific meetings, seems to support our findings. It might

be useful to develop an option grid or decision making tool in order to offer independent counseling and encourage shared decision making.

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SUPPLEMENTARY MATERIALS

APPENDIX 1. QUESTIONNAIRES SENT TO GYNECOLOGISTS WORKING IN UAE+ AND UAE- HOSPITALS.

1. Do you counsel patients who are eligible for UAE?

0 (never)----------10 (always)

a. If the answer is yes, please estimate the total number of patients you have counseled yearly.

0----------100

2. Do you refer patients who are eligible for UAE to the interventional radiologist?

0(yes)----------10 (no)

a. If the answer is yes, please estimate the total number of patients you have referred yearly.

0----------100

3. Would you consider the following characteristics a contra-indication for UAE?

0(yes)----------10 (no)

a. Type 7 subserosal pedunculated fibroid
b. Type 2 submucosal fibroid not eligible for trans cervical resection.
c. Patients with dysmenorrhea, but absence of heavy menstrual bleeding
d. Patients with suspected concurrent adenomyosis
e. Patients with an uterus > 20 weeks of gestation
f. Patients with a wish to conceive

4. Are there any other factors you consider a contra-indication for counseling patients for UAE?

5. Are patients who are scheduled for a UAE also scheduled for an introductory meeting with their treating physician (Interventional radiologist)? Yes/no

(for UAE- Do you think an interventional radiologists should be involved in the counseling process? Yes/No)

6. Does your hospital have a pain protocol for patients undergoing UAE? Yes/no

a. if the answer is yes, what is the content of this protocol? – Oral medication (NSAID, Paracetamol)– patients controlled analgesia pump – Epidural –other

7. Do you perform hysterectomies? Yes/no

a. If yes, please estimate how many you perform yearly?

8. Since 2013 the National guideline heavy menstrual bleeding was updated and included UAE as a treatment option in patients with symptomatic fibroids. Following publication of this guideline, did any changes occur in your hospital? If yes, please illustrate with an example.
9. Do you think that (every patient eligible for UAE) everybody should be counseled for UAE? Yes/No
10. Do you have doubts about the effectiveness of UAE? Yes/No
11. Do you wish to transfer care to another spcialist if this is necessary for the treatment?
12. Which items do you discuss during counseling for UAE? (choosing more options is possible)
10.1 UAE causes more pain after treatment than other treatments.
10.2 UAE patients recover faster than hysterectomy patients and resume work faster.
10.3 After a successful UAE, there is a 50% chance of secondary hysterectomy.
10.4 Hysterectomy and UAE offers comparable improvement of health related quality of life and patients satisfaction.

12. Do you have sufficient knowledge concerning the UAE procedure and outcomes to appropriately counsel your patients? Yes/no
12.1 If no, please offer possible improvement suggestions as how to improve UAE knowledge and implementation.

13. Which problems do you encounter in daily practice when counseling or planning an UAE?
(choosing more options is possible)
13.1 I do not counsel for UAE
13.2 The patient does not choose to have UAE.
13.3 I do not wish to refer my patient
13.4 Logistics are too complicated.
13.5 UAE is too painful

4

Uterine Artery Embolization in Women with Symptomatic Cervical Leiomyomata: Efficacy and Safety

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ABSTRACT

PURPOSE

To perform an evaluation on safety and efficacy of uterine artery embolization (UAE) in the patients with symptomatic cervical leiomyomata.

METHODS

Patients with symptomatic cervical leiomyomata who underwent UAE in one specialized hospital were retrospectively analyzed, both clinically and with MR imaging. The 3-month outcomes were assessed with MR imaging and a validated questionnaire. Long-term follow-up was assessed by direct contact or file review. To determine the efficacy of UAE for cervical leiomyomata, the primary objective was to assess the clinical outcome with the UFS-QOL questionnaire, containing the health related quality of life (HRQOL) and symptom severity score (SSS). To assess safety, the secondary objective included leiomyomata volume reduction, the infarction/ complication rate and secondary interventions were needed.

RESULTS

Between 2006 and 2017, eight of 1180 patients underwent UAE and were eligible for inclusion. All embolizations were technically successful (n = 8). At 3 months, all patients showed cervical leiomyomata volume reduction with a median reduction of 41.5% (38.8 cm3) compared to baseline (p = 0.012). No complications occurred. At a median follow-up of 3 months (range 1–7, n = 7), the HRQOL and SSS improved with a median difference of 13 points (range - 5 to 60, p = 0.063) and - 13 points (range - 79 to 3, p = 0.046), respectively. Long-term follow-up showed two secondary interventions (median of 43.5 months). Six patients reported no symptom recurrence.

CONCLUSION

UAE in women with symptomatic cervical leiomyomata is effective and safe with significant improvement in symptoms and quality of life. UAE is a valuable option for women seeking a non-surgical solution.

INTRODUCTION

Uterine leiomyomata are common benign tumors originating from neoplastic transformation of smooth muscle cells in the uterine wall [1]. Approximately 20–40% of women are affected in their reproductive age [2]. Uterine leiomyomata located in the cervix are rare, ranging from 0.9 to 8% of all uteri containing leiomyomata [3-5]. Symptoms associated with cervical leiomyomata are abnormal bleeding, pain (dysmenorrhea) and bulk-related symptoms [6]. Surgical treatment of cervical leiomyomata is difficult due to its location. Poor access to the operating field, suturing difficulty, poor cervical flexibility, increased blood loss and close neighboring organs (bladder, ureter and rectum) could hamper the procedure [7, 8]. UAE is an established valuable treatment alternative to surgery in the treatment of uterine fibroids located in the body or fundus of the uterus as reported in multiple randomized controlled trials [9-14]. Identification of the cervical vessels is complex and often differs in shape, size and location. Literature describes that the branches running toward the cervix are significantly variable in patients and shows that the vascular supply of the cervix seems to come from several vessels; however, these findings are based on postmortem studies [15-18]. Therefore, the localization of the afferent artery to the cervical perifibroid plexus is challenging. The aim of our study was to evaluate the efficacy and safety of UAE in the treatment of symptomatic cervical leiomyomata. This was achieved by using the validated standard UFS-QOL questionnaire including the health-related quality of life (HRQOL) and symptom severity score (SSS) [19, 20]. In addition imaging outcomes, complications and secondary interventions were evaluated.

MATERIALS AND METHODS

STUDY DESIGN

This retrospective study evaluated all patients that underwent UAE for cervical leiomyomata from 2006 until 2017 in a single specialized hospital in the Netherlands. To determine the efficacy of UAE for cervical leiomyomata, the primary objective was to assess the clinical outcome using the validated standardized questionnaire Uterine Fibroid Symptom and Health-related Quality of Life (UFSQOL) at baseline and at 3 months after UAE, containing the health-related quality of life (HRQOL) and symptom severity score (SSS). To assess safety, the secondaryobjective included cervical leiomyomata volume reduction, the infarction/complication rate and secondary interventions needed. Inclusion criteria were (1) patients with leiomyomata-related complaints, i.e., abnormal uterine bleeding, pain (dysmenorrhea) and/or bulk-related symptoms, (2) MR imaging which confirmed the presence of a cervical leiomyomata with or

without other uterine body leiomyomata, (3) leiomyomata treated with UAE and (4) the availability of 3 months post-embolization MR images. Exclusion criteria were (1) UAE during pregnancy and (2) UAE for postpartum hemorrhage. The local ethics committee approved this study. All patients gave their informed consent for retrospective review with a waiver for patients who were unable to be located.

STUDY MEASURES

Magnetic Resonance Imaging (MRI) at baseline and follow-up (short term; long term)

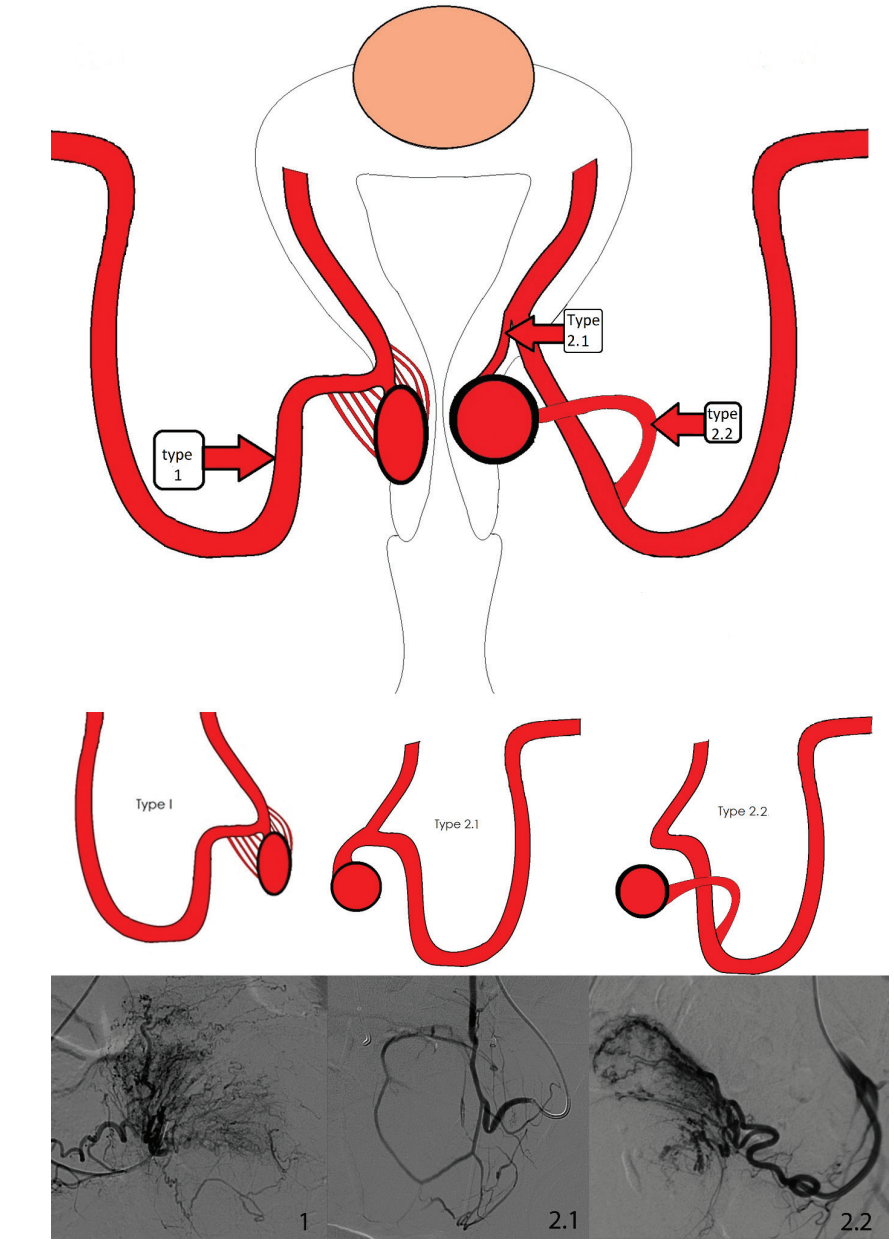
All patients included underwent T1, T2 and T1 contrastenhanced (gadolinium) MR imaging at baseline and at 3 months following UAE. The diagnosis of a cervical leiomyomata was determined with MR imaging with the criterion of leiomyomata location at the cervix (intramural/ submucous/subserous) or attachment (pedunculated) to the cervix. Fibroid volume was calculated using the ellipsoid formula: length 9 width 9 height 9 0.5233. Two radiologists assessed after UAE the infarction rate by using the same volumetric measurement as mentioned above [21]. Insufficient infarction was determined at a cutoff point of 80% as described earlier by Smeets et al [22].

ANGIOGRAPHIC PROCEDURE

UAE was performed according to local protocol and professional standards and reported as described by Goodwin et al. [23] All patients received a drip infusion at the wrist and an intravenous patient-controlled analgesia pump for pain management. All UAE consisted of bilateral access in the common femoral arteries with placement of the 4Fr sheath and selective placement of a C2 catheter (Tempo Aqua C2, Cordis Corporation, Miami, USA) in both uterine arteries. Digital subtraction angiography (DSA) displayed the cervical leiomyomata vascularity. According to Kim et al. [24], the cervical leiomyomatas were classified based on vascular aspects during DSA: Grade I poor/minimal vascularity, without enhancement of the tumor; Grade II moderate vascularity, with limited enhancement in small vessels intratumorally; and Grade III pronounced staining of the leiomyomata, with large tortuous vessels. In addition to these intratumoral vascularity patterns, an overview is made of two types of afferent arteries identified during DSA (Fig. 1). Due to a lack of available information (sometimes lack of detailed DSA images of the previous procedures) and overprojection of Grade III tortuous vessels, not all the patients could be classified. However, the radiologists performing the embolization procedures

described the different types of afferent arteries as seen during the procedures in their reports. Ideally, a catheterization technique was applied when possible with superselective placement of the (micro-)catheter tip into the uterine artery side branch, i.e., a separate cervical artery, in order to secure optimal embolization of the cervical leiomyomata. Initial treatment was focused on super-selective UAE of the cervical fibroid followed by standard UAE of the remaining uterine fibroids when present. Figure 1 displays an overview of the different afferent arteries and the location of the catheter during UAE. Described in this cohort is the dominant side of the afferent artery. Type 1 is an often seen entity, wherein not only one afferent artery can be identified due to overprojection of an arterial plexus. Potentially, there is no solitary afferent artery, but only a plexus feeding the cervical leiomyomata. In Type 1 cases with an arterial plexus, the catheter tip was positioned at point A. Type 2 was identified in 3 cases, defined as a cervical leiomyomata with a single uterine artery branch, i.e., a solitary feeding cervical artery. In Type 2 cases, when possible, super-selective positioning of the catheter tip was applied into the afferent cervical artery. Type 2.1 is a solitary side branch originating proximal from the ascending segment of the uterine artery. Type 2.2 is a distal solitary side branch of the uterine artery. The embolization agents used were precisely calibrated microspheres, built of a hydrogel core and coated with a polymer Polyzene_-F (Embozene TM, Boston Scientific, Amsterdam, The Netherlands) ranging in size from 500 to 1200 lm and additionally 700 lm non-spherical polyvinyl alcohol (PVA) particles in one patient (Contour TM, Boston Scientific, Amsterdam, The Netherlands). The angiographic embolization endpoint was at complete stasis. All patients received a periprocedural intravenous patient controlled analgesia pump, for adequate pain treatment. Complications were recorded.

FIGURE. 1 Overview of afferent branching arteries to cervical leiomyomata as identified during UAE.



Note; Boxes type 1, 2.1 and 2.2 are the locations of the catheters as used per subtype. Subtype 1 with a plexus of feeding branches to the cervical leiomyomata. Subtype 2.1 with a proximal single branch from uterine artery to the cervical leiomyomata. Subtype 2.2 with a distal single branch from uterine artery to the cervical leiomyomata. Type 2 cases were, when possible, superselectively catheterized

CLINICAL ASSESSMENT AT BASELINE AND FOLLOW-UP (SHORT TERM AND LONG TERM)

Patients completed the standardized questionnaire, Uterine Fibroid Symptom and Health-related Quality of Life (UFSQOL) at baseline and at 3 months after UAE.[20, 25] Adverse events were recorded. Long-term clinical results were also obtained through a telephone-administered questionnaire and reviewing patients' files. The UFS-QOL rates the SSS on a scale of 0–100 and the HRQOL on a scale of 0–100 in seven different domains: (1) concern, (2) activities, (3) energy/mood, (4) control, (5) self-consciousness, (6) sexual function and (7) HRQOL total score. [20] A lower SSS means improvement in symptoms. A higher HRQOL score indicates better quality of life. The duration of hospital stay was recorded.

STATISTICAL ANALYSIS

The Wilcoxon signed-rank test for paired samples was used to compare the cervical leiomyomata volumes, the UFSQOL including HRQOL and symptoms severity scores (SSS) during follow-up and at baseline. P values < 0.05 were considered statistically significant. SPSS (IBM SPSS Statistics, version 22) was used for statistical analysis.

RESULTS

From a total of 1180 patients who underwent UAE during 2006 until 2017, 12 patients with proven cervical leiomyomata on MRI underwent UAE. Four of these patients were excluded due to pregnancy (n = 1), postpartum (n = 1), UAE of an acute bleeding leiomyomata expulsion as preparation for surgical removal (n = 1) and absence of a follow-up MRI (n = 1). The median age of all patients (n = 8) at baseline was 37.0 years, ranging from 33 to 47 years. Three patients showed concurrent non-cervical fibroid disease (Table 1, patients 6, 7 and 8). Table 1 lists baseline characteristics of these patients with symptomatic cervical leiomyomata (demographics, previous treatment, symptoms and concurrent leiomyomata) who underwent UAE (procedural characteristics). All eight UAEs were technically successful without complications. All patients were discharged from the hospital the next day, except one patient who needed one extra night due to persistent pain. After 3 months, one patient reported transient amenorrhea.

TABLE 1. patient demographics and procedural characteristics

Patient demographics, previous treatment, symptoms				Procedural characteristics		
Patient	**age**	**Previous treatment**	**Main symptoms**	**Catheter**	**UAE material**	**Hospital stay**
1	33	Hormonal (oral)	BRS + WTC	4Fr sheath + C2	microspheres 900 – 1100 µm	1
2	37	NR	AUB + WTC	4 Fr sheath + C2	Super selective. Microspheres 500, 700, 900 µm (only left side)	1
3	33	Tranexamic acid, Ulipristal. Myomectomy 2007 and 2015.	BRS + WTC	4 Fr sheath + C2	microspheres 700, 900, 1300 µm and 700 µm PVA	1
4	45	NR	BRS	4 Fr sheath + C2	microspheres 700-900 µm	1
5	38	Hormonal (oral)	P	4Fr sheath + C2	microspheres 500, 900 µm	1
6+	47	NR	AUB + BRS	4 Fr sheath +C2	microspheres 700, 900, 1200	1
7+	42	no	AUB	4 Fr sheath + C2	microspheres 700-900 µm and 900-1200 µm	3
8+	33	Hormonal (oral)	P + AUB	4Fr sheath + C2	microspheres 700-900 µm	1
median (range)	**37.5 (33-47)**					**1.0 (1-3)**

Note: + with concurrent non-cervical leiomyoma disease. NR=not reported. AUB=abnormal uterine bleeding, BRS=bulk related symptoms, WTC=wish to conceive, P= Intermittent pain not related to the menstrual cycle.

IMAGING RESULTS

All patients demonstrated volume reduction compared to baseline at 3 months after UAE (Table 2). Figure 2 displays a median leiomyomata volume reduction of 41.5% (38.8 cm3) at 3 months compared to baseline (p = 0.012). Five out of eight patients (62.4%) displayed C 80% infarction of the cervical leiomyomata. The grade pattern of these patients is displayed in Table 2. Three patients (no. 1, 7 and 8) demonstrated 50, 40 and 60% infarction of the cervical leiomyomata, respectively (Table 2). All of these patients had a Grade III leiomyomata. Three out of eight patients (no. 6, 7 and 8) demonstrated concurrent non-cervical leiomyomata disease, and two of them (no. 7 and 8) received additional treatment. These two patients showed a cervical leiomyomata infarction rate

of 40% and 60%. In patient no. 8, a concurrent anterior wall leiomyomata showed no infarction after the first UAE. Follow-up MRI demonstrated an unchanged uterine body leiomyomata and progressive enhancement of the cervical leiomyomata overtime. Results of the (technically successful) secondary UAE showed no additional infarction rate on the follow-up MRI. Patient no. 7 showed an infarction rate of 40% (cervical leiomyomata) after the initial UAE, with a volume reduction of nearly 63% (216.7 cm3). Due to persisting gynecological symptoms with complaints of mass effect, hysterectomy was eventually carried out. Figures 3 and 4 display the image changes in terms of aspect, volumes and contrast enhancement of cervical leiomyomata after UAE in patient no. 2 and 6

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FIGURE 2. Median cervical leiomyomata volume reduction (cm^3) until 3 months of follow-up compared to baseline

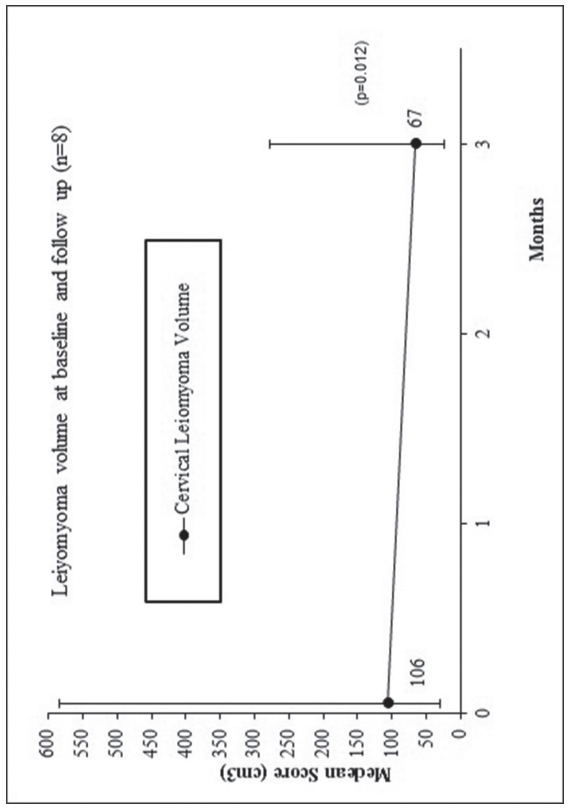
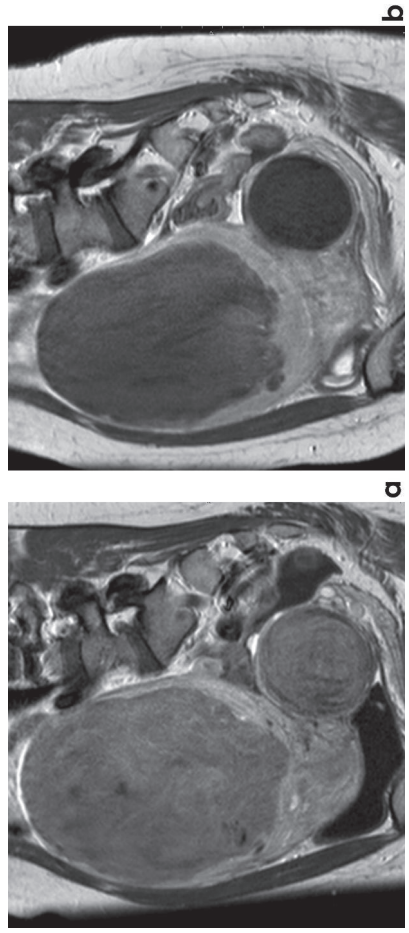


FIGURE 3. MRI (SAG T1 - TSE - HR contrast +) imaging of cervical leiomyomatas in combination with uterine body fibroids



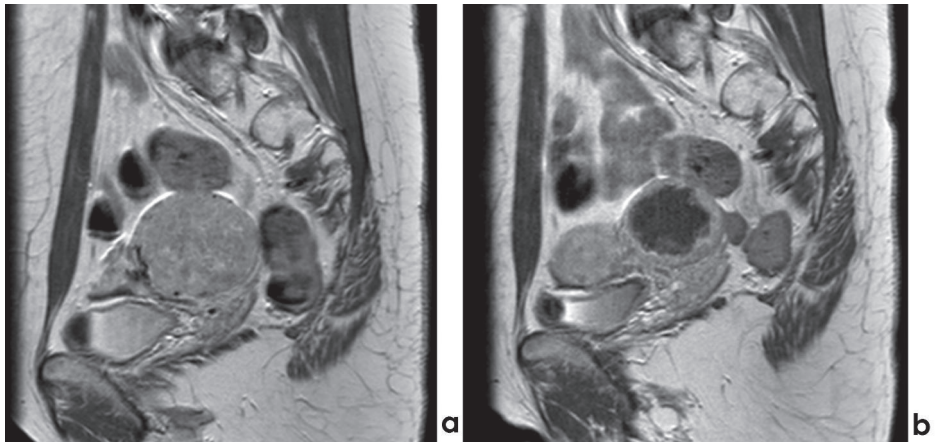
*note: Patient no. 6, MR images (sagittal T1-TSE-HR + contrast) of leiomyomata in the uterine body and cervix. **(a)** Both the cervical leiomyoma (106 cm3) and the uterine body leiomyoma demonstrated full enhancement prior to UAE. **(b)** Follow-up imaging 3 months after UAE with 5% enhancement of the leiomyoma in the uterine body and no enhancement of the cervical leiomyoma, as a result of complete infarction after bilateral UAE (2cc700 µm, 4cc900 µm and 4cc1200 µm microspheres, EmbozeneTM). The cervical leiomyoma volume three months after UAE was 77 cm3 with a volume reduction of 27 %.

TABLE 2. Imaging characteristics at baseline and follow-up

	Baseline				3-month follow-up					
Patient	**Grade**	**Size (cm)**	**Volume (cm3)**	***Body fibroid Volume (cm3)***	**Size (cm)**	**Volume (cm3)**	**Volume decrease**	**Infarction rate**	**Body fibroid volume reduction**	***Body fibroid Infarction rate***
Patients with solitary cervical leiomyoma										
1	3	8.4*8.6*7.8	294.86	-	6.4*6.7*5.5	123.41	58.1%	50%	NA	NA
2	3	5.9*6.1*5.6	105.47	-	4.4*4.9*5.0	56.41	46.5%	95%	NA	NA
3	3	7*8*12.8	375.1	-	5.7*8.1*11.5	277.85	25.9%	80%	NA	NA
4	3	6.0*5.6*5.1	89.67	-	4.9*4.1*3.8	39.95	55.5%	90%	NA	NA
5	1	5.8*4.3*4.1	53.50	-	4.4*4.1*3.6	33.98	36.5%	100%	NA	NA
Median (range)			105.5 (53.5-375.1)			56.4 (34.0-277.9)	46.5% (25.9-58.1)	90% (50-100)		
Patients with concurrent non-cervical fibroid disease										
6	2	7.2*5.2*5.4	105.80	837.71	5.0*4.4*6.7	77.13	27.1%	100%	21.6%	95%
7#	3	11.5*9.7*10.0	583.74	1: 9.18 2: 14.13 3: 3.3	7.5*8.0*6.9	216.65	62,9%	40%	1: 73.4% 2: 37.4% 3: 48.5%	1:100% 2:100% 3:100%
8#	3	3.4*3.6*4.6	29,46	1:6.88 2: 59.77	3.4*3.2*4.1	23.34	20.8%	60%	1: 34.0% 2: 26.1%	1: 90% 2: 0%
Median (range)			105.8 (29.5-583.7)			77.1 (23.3-216.7)	27.1% (20.8-62.9)	60% (40-100)		
Total of patients										
Total Median (range)			105.6 (29.46-583.8)			66.8 (23.3-277.9)	41.5% (20.8-62.9)		85% (40-100)	

*note: NA not applicable
Patient underwent secondary intervention

FIGURE 4. MRI (SAG T1-TSE-HR contrast +) imaging of a solitary cervical leiomyoma

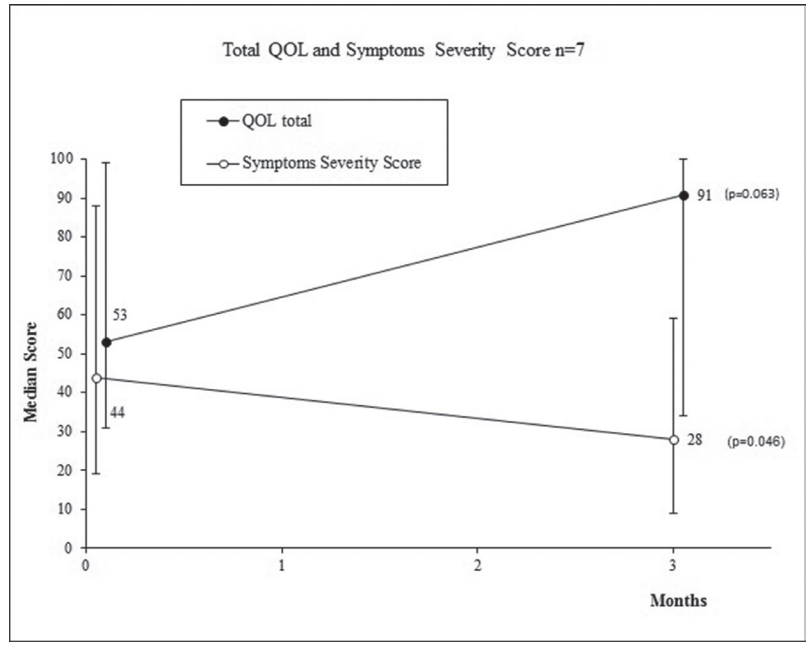


*note: Patient no. 2, MR images (sagittal T1-TSE-HR + contrast) of a single cervical leiomyoma in a 37 year old patient with heavy menstrual blood loss and a wish to conceive. Cervix with a broad-based leiomyoma on the left. **(a)** The cervical leiomyoma (106 cm3) with full enhancement prior to UAE. **(b)** MR imaging 3 months after UAE showed 95% infarction with an irregular enhancing rim. Unilateral left side UAE with 2cc500, 2cc700 and 3cc900µm microspheres EmbozeneTM; 47% volume reduction (56.4 cm^3)

CLINICAL RESULTS UFS-QOL: SHORT TERM.

Seven of eight included women filled out the UFS-QOL at a median follow-up of 3 months (range 1–7). Figure 5 depicts the median HRQOL and SSS (both on a total scale of 100 points) at baseline and follow-up. The total HRQOL score showed a median, nonsignificant increase of 13 points (range - 5 to 60; p = 0.063). The SSS demonstrated a statistically significant improvement compared to baseline and decreased with a median score of - 13 points (range - 79 to 3; p = 0.046). Appendix 1 in electronic supplementary material displays the median score of the separate domains. It shows an increase in HRQOL scores in every domain; however, only sub-domains concern (p = 0.043), control (p = 0.046) and self-consciousness (p = 0.042) reached statistical significance.

FIGURE 5. Total quality of life and symptoms severity scores at baseline and 3 months follow-up



CLINICAL OUTCOMES: LONG TERM.

Long-term clinical follow-up with a median of 43.5 months (range 6–127, n = 8) outlined the two secondary treatment cases. Patient no. 8 with concurrent noncervical uterine leiomyomata disease received a second UAE at 15 months due to recurrent pain after 12 months. At 17 months following the second UAE, she returned again because of pain in the left lower abdomen. At 107 months after the second UAE, no additional treatment was necessary and reported symptoms to be manageable. Patient no. 7 needed a hysterectomy at 72 months after UAE due to cervical leiomyomata growth and clinical symptom recurrence. Patient no. 5 with reported worsening of HRQOL and limited improvement in symptoms in short term became asymptomatic on long-term follow-up (45 months). The remaining patients (n = 6, 75%) reported no additional treatments needed nor symptom recurrence at a median follow-up of 38.0 months (range 6–125). No adverse events were reported.

DISCUSSION

SUMMARY OF CLINICAL FINDINGS

This retrospective study demonstrated the efficacy and safety of UAE in women with symptomatic cervical leiomyomata, based on clinical outcomes with HRQOL, symptom severity scoring (SSS) and MR imaging. Significant reduction in the cervical leiomyomata volume was calculated related to a statistically significant decrease in the SSS at 3 months after UAE. Short-term improvement in symptom severity and HRQOL seems to be largest in the women with concurrent non-cervical leiomyomata disease. However, long-term outcomes displayed that this effect was not maintained. UAE infarction rates were ranging between 40 and 100%. Six out of eight patients underwent a successful cervical leiomyomata UAE treatment. All of these patients with the exception of one showed a leiomyomata infarction rate of more than 80%. Two of three patients with concurrent non-cervical leiomyomata disease received additional therapy because of recurrent or persisting symptoms. No complications occurred.

INTERPRETATIONS OF OUTCOMES

Patients with a solitary cervical leiomyomata showed lower median improvement in HRQOL and symptom severity at short-term follow-up compared to women with concomitant uterine fibroids. This could be explained by the limited number of patients in this study and the effect of two patients with solitary cervical leiomyomata demonstrating low UFS-QOL scores, which may be explained by a lower infarction rate and accompanying non-cervical leiomyomata disease. As suggested by Aryani et al. [26], a potential cause of insufficient cervical leiomyomata infarction could be preexistent collaterals potentially also feeding the cervical leiomyomata. This was unfortunately not verifiable, because no specific DSA examination of the internal iliac arteries with their anterior divisions to the pelvis with potential collaterals was performed during the UAE procedures. Another cause of incomplete infarction might be the hypervascularity of the body/fundal leiomyomata, in which case the embolic agent might migrate to the uterus instead.

STRENGTHS AND LIMITATIONS

This is the second retrospective study published about UAE in women with symptomatic cervical leiomyomata, Kim et al.'s being the first. [24]. Our study retrospectively examined the clinical outcome before and after UAE obtained by validated questionnaires, which were prospectively collected. All available imaging was evaluated by two radiologists, making outcomes more reliable.

Only eight patients were included in this study, resulting in a limited sample size. Therefore, although the UAE results in symptomatic cervical leiomyomata favor this option as a treatment for women seeking uterine-sparing surgery, the limited sample size does not allow us to draw too strong conclusions. Larger high-quality trials should be conducted to confirm our results. However, this condition is rare; thus, reports like these remain important when counseling these patients.

COMPARISON WITH OTHER STUDIES

We are aware of two reports [24, 27] on UAE in the treatment of cervical leiomyomata. The first report compared effectiveness of UAE of cervical leiomyomata versus uterine fundal/body leiomyomata with imaging and stated that ''the results of UAE were disappointing, indicating a need for caution in selecting and counseling patients for this treatment '' [24]. At 3 months they reported a total infarction infarction in only 2/10 (20%) patients and zero infarction in 2/10 (20%) patients, with symptom improvement in 4/10 (40%) patients. They did not use a standardized validated questionnaire. Five out of nine patients showed a Grade I vascularity pattern, two Grade II and two Grade III vascularity pattern. Our cohort consists of eight patients with six Grade III vascularity patterns, one Grade II and one Grade I vascularity pattern. Our study results demonstrated a higher treatment success rate. At 3 months, the symptom severity score (SSS) and HRQOL score improved in 7/7 patients (100%) and 5/7 patients (71%), respectively. Long-term satisfaction without additional therapy was achieved in 6/8 patients (75%). The difference in success rate may be explained by the leiomyomata vascularity (Grade III), a different UAE agent and the relatively larger size, and therefore, the relatively increased vascularization which might presumably lead to increased infarction compared to infarction rates of smaller fibroids with less vascularization and/or the described catheterization technique. The second publication concerns the world's first reported UAE during pregnancy. [27] We hypothesized that the pregnancy itself would be an influencing factor on the cervical leiomyoma growth, which is why we excluded pregnant or postpartum patients in this study [28].

CONCLUSION

UAE in women with symptomatic cervical leiomyomata seems to be effective and safe with significant improvement in symptoms and quality of life. UAE is a valuable option for women seeking a non-surgical solution.

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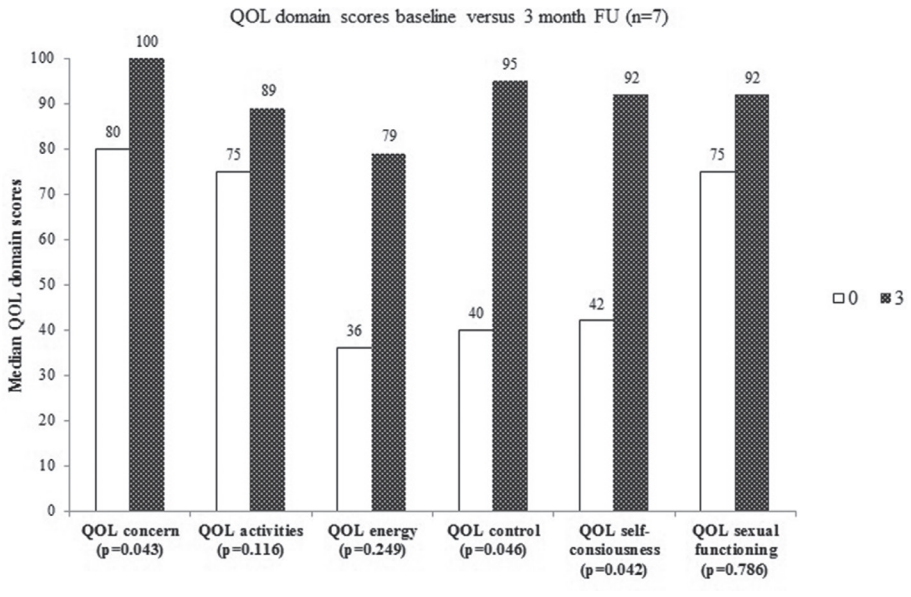
SUPPLEMENTARY MATERIALS

APPENDIX 1. Median quality of life subdomain scores at baseline and 3 months follow-up



PART II

UAE AS A TREATMENT IN PATIENTS WITH ADENOMYOSIS AND TOWARD STANDARDIZATION OF ULTRASONOGRAPHY IN DIAGNOSING ADENOMYOSIS

5

Uterine Artery Embolization for Symptomatic Adenomyosis: 7-Year Clinical Follow-up Using UFS-QoL Questionnaire

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ABSTRACT

PURPOSE

The purpose of this study was to assess clinical outcomes 7 years after uterine artery embolization (UAE) in the treatment of symptomatic adenomyosis.

MATERIALS AND METHODS

In this prospective cohort study, one specialized hospital in the Netherlands recruited patients with symptomatic adenomyosis or adenomyosis in combination with fibroids for UAE. The 7-year post-intervention outcomes were health-related quality of life (HRQOL), symptom severity scores (SSS), satisfaction, menopause and re-interventions.

RESULTS

Twenty-nine patients with adenomyosis (15 with fibroids) were treated with UAE between September 2006 and January 2010. The 7-year questionnaire was mailed in November 2016. The mean follow-up was 95 months (SD 9.0) at a mean age of 50 (SD 5.4). Questionnaires were returned by 24/29 patients (83%). The remaining five patients were contacted through telephone. One of these patients was untraceable. Seven years after treatment 5 of 28 patients (18%) underwent a secondary hysterectomy. The HRQOL and SSS scores as measured by UFS-QOL at 3 months after UAE showed significant improvement of -57 points (score: 15) and ?40 points (score: 91), respectively. These scores remained comparable stable up unto 7 years. The SSS showed a significant difference of 17 points (0–100) in favor of the adenomyosis in combination with fibroids group (p = 0.020). Menopause was reported by 10/28 patients (36%). Twenty-one of 29 (72%) patients declared to be at least fairly satisfied about UAE.

CONCLUSION

After 7 years of follow-up, in 82% of UAE treated patients with symptomatic adenomyosis a hysterectomy was avoided.

INTRODUCTION

Adenomyosis is a benign disease characterized by the presence of ectopic endometrial glands and stroma which causes reactive hypertrophy of the myometrium [1, 2]. Uterine artery embolization (UAE) was first described in 1995 for the treatment of uterine fibroids [3]. It has been established as a valuable treatment option for patients with symptomatic uterine fibroids [4-6]. Since then uterine artery embolization is being explored as a possible treatment option for adenomyosis and seems to have a favorable outcome in multiple case series, although randomized controlled trials are lacking [7-14]. Earlier we reported the result of uterine artery embolization in the treatment of symptomatic therapy-resistant adenomyosis with 3-year follow-up. In that study, we analyzed clinical outcomes, health-related quality of life (HRQOL), symptom severity scores (SSS), menopause and satisfaction [15]. This 37-month follow-up reported preservation of the uterus in 28/29 patients (97%) with good clinical outcome. It is important to extent the follow-up period in order to further expand upon these outcomes.The purpose of this study was to assess clinical outcomes 7 years after uterine artery embolization in the treatment of symptomatic adenomyosis in 29 patients with pure adenomyosis (n = 14) or adenomyosis with fibroids (n = 15).

MATERIALS AND METHODS

STUDY DESIGN

The detailed methods in terms of inclusion criteria, exclusion criteria, MRI criteria, UAE procedures and UFS-QOL description of this study have been reported earlier [15]. In short, this prospective cohort study was conducted in one hospital in the Netherlands. It evaluated 234 symptomatic patients (abnormal menstrual bleeding, pelvic pain, and bulk-related symptoms) who presented between 2006 and 2010. Patients with MRI confirmed (junctional zone [12 mm) pure adenomyosis or adenomyosis in combination with fibroids were asked to participate in the study. This 7-year follow-up study was approved by the local ethics committee. All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Patients gave their informed consent and filled out the standardized questionnaire.

STUDY MEASURES

During the 3-year follow-up, patients received three similar HRQOL and SSS questionnaires (UFS-QOL) at different points in time. The 7-year questionnaire evaluated re-intervention rates, menopause, patient satisfaction, SSS and HRQOL

and was sent approximately 7 years after the last patients were treated. If patients did not respond to the questionnaires telephone contact was attempted, we inquired about participation, additional treatment and patient satisfaction.

HRQOL and SSS

The UFS-QOL questionnaire was used to evaluated HRQOL and SSS. A higher HRQOL score means a better quality of life. A lower SSS stands for improvement of symptoms. As described earlier, patients with a SSS<20 in combination with an total HRQOL score >80 were considered asymptomatic [15].

Menopause

We inquired whether the patient went through menopause (the absence of menstrual periods for at least 12 months). Patients could choose from the answers ''yes,'' ''no'' or ''I don't know.'' The last was applicable to patients who underwent hysterectomy or displayed amenorrhea after uterine artery embolization.

Satisfaction

Patients were asked to indicate how satisfied they were with the received treatment on a 7-point Likert scale: ''very satisfied,'' ''fairly satisfied,'' ''not satisfied, nor unsatisfied,'' ''fairly unsatisfied,'' ''unsatisfied'' or ''very unsatisfied.'' We also inquired whether patients would recommend the primary treatment to a friend and whether or not they would have chosen uterine artery embolization again if they would have the opportunity to do so.

Statistical analysis

We used SPSS statistical software (version 22) for analyses. Comparison of differences between groups was assessed with the Mann–Whitney U test. Longitudinal differences between 3 and 7 years of follow-up were evaluated using the Wilcoxon signed-rank test. Hysterectomy timing during 7 years of follow-up was examined with Kaplan Mayer survival analysis. A probability <0.05 was considered statistically significant.

RESULTS

Baseline results and outcomes until 3 years of follow-up were reported previously [15]. Table 1 presents an overview of these outcomes. A total of 29 women were enrolled: 14 patients with pure adenomyosis and 15 patients with combined adenomyosis/fibroids. Median baseline HRQOL scores in the pure adenomyosis and adenomyosis combined with fibroids group were comparable (p = 0.076). Median baseline SSS was significantly higher (=worse) in the pure adenomyosis group compared to the adenomyosis with fibroids group (p = 0.036). At 3 and 37 months of follow-up,HRQOL and SSS were comparable.

TABLE 1. Clinical follow-up at baseline, 3 months, 3 year and seven years

	Baseline	**3 months**	**3-year**	**7-year**
Patients with adenomyosis (n=29)	Pure: n=14 Combined: n=15	Pure: n=13 Combined: n=15	Pure: n=13 Combined: n=15	Pure: n=10 Combined: n=11
SSS				
P value	p=0.036	p=0.835	p=0.382	p=0.020
Pure adenomyosis (median)	78.2	18.8	15.6	17.2
Adenomyosis with fibroids (median)	62.4	15.6	6.3	0
Overall (median, range)	72 (23-100)	15 (0-66)	17 (0-34)	17.2 (0-43.8)
HRQOL				
HRQOL	p=0.076	p=0.769	p=0.091	p= 0.379
Pure adenomyosis (median)	37.9	91.4	89.7	95.3
Adenomyosis with fibroids (median, range)	53.0	87.1	99.1	99.1
Overall (median, range)	51 (20-88)	91 (55-100)	99 (29-100)	98.3 (9-100)
Additional treatment				
Secondary embolization	NA	NA	3 (1x pure group, 2x combined group)	Status quo
Secondary hysterectomy	NA	NA	1 (pure group)	4 (2x pure group, 2x combined group)

*Note: Median SSS, HRQOL scores and additional treatment
NA, not applicable; pure, only adenomyosis; combined, adenomyosis with concurrent fibroids

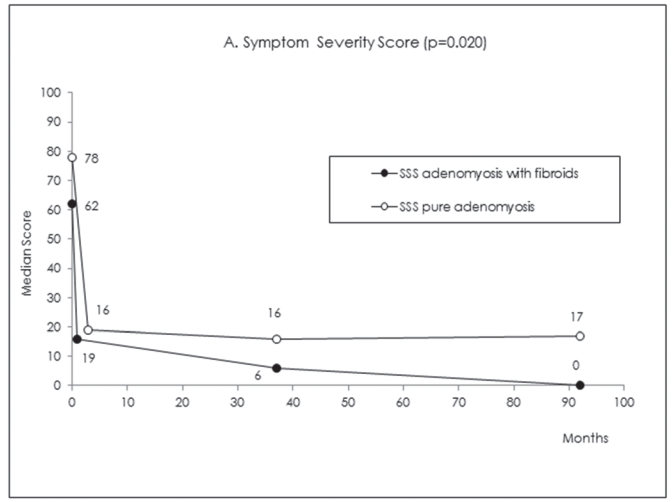
PATIENTS

The mean follow-up duration was 7.4 years (SD 0.83) at an overall mean age of 50.5 (SD 5.5). The mean age of patients in the pure adenomyosis and the adenomyosis with fibroids group was 48.8 (SD 7.1) and 51 (SD 4.6), respectively. Questionnaires were returned in 24/29 patients (83%). This included three patients who underwent secondary hysterectomy and therefore could not fill out the complete questionnaire. Completed questionnaires were returned in 21/29 patients (72%). These 21 filled in questionnaires were divided into 10 questionnaires from patients in the pure adenomyosis group and 11 questionnaires in the adenomyosis with fibroids group. We contacted the five non-responders by telephone and inquired about participation, additional treatment received, recommendation to a friend and satisfaction. Two of the non-responders underwent a secondary hysterectomy due to persisting symptoms, two patients (pure adenomyosis n = 1 and adenomyosis with fibroids n = 1) did not have a recurrence of symptoms, but declined full questionnaire participation and one patient was untraceable. These patients did answer the satisfaction questions concerning UAE.

CLINICAL OUTCOME, HRQOL AND SSS AT 37 MONTH FOLLOW-UP, AS ALREADY REPORTED [15]

In the earlier reported 37-month follow-up, three patients underwent a second UAE at 6, 7, and 14 months and one patient received a secondary hysterectomy at 17 months following UAE. The second embolizations were carried out in one patient with pure adenomyosis and in two patients with adenomyosis and fibroids. The hysterectomy occurred in a patient with pure adenomyosis. Of 29 patients, 22 (76%) reported to be asymptomatic and seven patients reported to have persisting mild symptoms without additional therapy. Four of these seven patients had pure adenomyosis. Mean HRQOL scores are displayed in Table 1. Longitudinal analysis revealed improvement between baseline and 3-month follow-up (HRQOL: p<0.001; Symptoms Severity: p\0.001). During the 3–37-month interval, SSS improved further (p = 0.005) and HRQOL stabilized. Scores over time are displayed in Fig. 1.

FIGURE 1. Median SSS and HRQOL at baseline, 3, 37 and 92 months. A. Median SSS. B. Median HRQOL



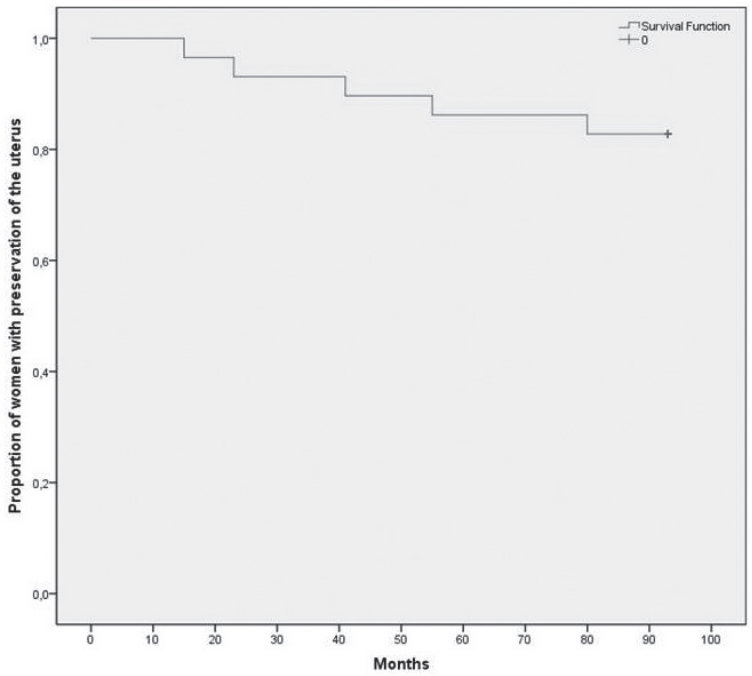
*Note: both figures depict two groups: patients (n=10) with pure adenomyosis and patients (n=11) with adenomyosis and fibroids (excluding two patients who declined questionnaire participation, five patients who underwent hysterectomy and one patient who was untraceable).

CLINICAL OUTCOME, HRQOL AND SSS AT 7 YEARS

At 7-year follow-up, four additional women had hysterectomy performed at 23, 41, 55 and 80 months after UAE. Thus, in total five of 28 women underwent a secondary hysterectomy (Fig. 2). Resulting in avoidance of hysterectomy in 23/28 (82%) of patients. Three of the hysterectomies occurred in the pure

adenomyosis group (14, 23, 41 months) and two in the adenomyosis with fibroids group (55, 80 months). Seventeen of 23 (74%) patients with a preserved uterus were asymptomatic, four had persisting symptoms and two declined questionnaire participation. Persisting symptoms occurred in three patients with pure adenomyosis and in one patient with adenomyosis and fibroids. Overall median SSS in 21 patients was 6.3 (range 0–87.5) corresponding with a median HRQOL overall score of 98.3 (range 8.6–100) (Table 1). SSS, HRQOL scores and secondary interventions for patients with pure adenomyosis and adenomyosis with fibroids are depicted in Table 1. Figure 1 shows median HRQOL and SSS over time for both groups Statistical analysis shows no HRQOL differences between groups at 7-year follow-up (p = 0.379). The SSS shows a statistical difference in favor of the adenomyosis with fibroids group (p = 0.020).

FIGURE 2. Secondary hysterectomy rate during long term follow-up



Menopause

At 7 years, 28/28 patients answered the following menopause question. The question: ''did you experience absence of menstrual periods for at least 12 months?'' was answered ''yes'' by 10/28 patients (36%). ''No'' was answered by 8/28 patients (28.6%) and 10/28 patients (36%) answered ''I don't know''. The last group consisted of 6/28 (21%) patients who reported permanent amenorrhea directly following UAE and four patients who underwent hysterectomy and therefore do not have periods. There was no difference between pure adenomyosis and adenomyosis with fibroids (p = 0.380). Table 2 reports menopause outcomes per group.

TABLE 2. Menopause outcomes per group

	Pure adenomyosis (n=14)	Adenomyosis with fibroids (n=14)	*P* value
Yes *	6 (42.9%)	4 (28.6%)	
No *	4 (28.6%)	4 (28.6%)	0.380
I don't know *	4 (28.6%)	6 (42.9%)	

*Note: response to question ''did you experience absence of menstrual periods for at least 12 months?''

Satisfaction

At 7 years, 24/29 patients responded to questions concerning treatment satisfaction, advising UAE to a fiend and undergoing UAE again. Within groups, 11 patients in the pure adenomyosis group and 13 patients in the adenomyosis with fibroids group responded to the following questions. In five patients, we did not receive an answer. The majority of patients reported to be satisfied. Twelve out of twenty-nine (41%) patients were ''very satisfied'', 6/29 (21%) were ''satisfied'', 3/29 (10%) were ''fairly satisfied, 1/29 (4%) was ''fairly unsatisfied'' and 2/29 (7%) were ''very unsatisfied''. Overall, 21/29 (72%) patients were at least fairly satisfied about UAE, in 10/14 (71%) patients with pure adenomyosis and in 11/15 (73%) in patients with adenomyosis and fibroids (p = 0.552). Twenty of 28 patients (71%) would advise UAE to a friend. Three would not (11%) and one (4%) patient responded not to know. Twenty patients would again undergo UAE, three not and one did not know. There were no differences between groups as detailed in Table 3.

TABLE 3. Satisfaction outcomes per group

	Pure adenomyosis (n=11)	Adenomyosis with fibroids (n=13)	*P* value
Very satisfied	5 (35.7%)	7 (46.7%)	
Satisfied	2 (14.3%)	4 (26.7%)	
Fairly satisfied	3 (21.4%)	-	0.552
Fairly unsatisfied	-	1 (6.7%)	
Very unsatisfied	1 (7.1%)	1 (6.7%)	
Advise a friend	10 (71.4%)	10 (66.7%)	0.348
Repeat embolization	10 (71.4%)	10 (66.7%)	

DISCUSSION

MOST IMPORTANT CLINICAL FINDINGS AND INTERPRETATIONS OF OUTCOMES

Four of five patients had hysterectomy after the 37-month follow-up interval. The continued increase in patients undergoing hysterectomy underlines the importance of long-term follow-up. It could provide insights for prediction of quality of life, recurrence of symptoms, costs and possibly counseling of patients. The literature describes some varied secondary intervention and symptom improvement rates. Bae et al. followed up 50 patients with pure adenomyosis until 48 months after UAE and reported only one hysterectomy (at 18 months) and symptom improvement in 38/50 (76%) patients; however, this was not measured with a validated questionnaire. The secondary hysterectomy rate was not comparable to our study and could possibly be explained by; (1) the selected group of patients in our study with possibly worse baseline symptoms and no other option than a hysterectomy and 2) a longer follow-up than any other study in which we demonstrate that even at 55 and 80 months secondary hysterectomies are performed. Froeling et al. [16], that also used the UFS-QOL to measure HRQOL, reported a 2/7 hysterectomy rate in patients with pure adenomyosis and 2/10 hysterectomies rate in patients with adenomyosis and fibroids at a follow-up of 46 months. HRQOL scores were comparable to our study with a 44.0 score at baseline and 99.57 at 46 months of follow-up. The most noticeable improvement of HRQOL in patients with pure adenomyosis and in adenomyosis with fibroids occurred in the first 3 months after UAE and remained stable over time without differences between the two groups. SSS at baseline was significantly different in

favor of the adenomyosis combined with fibroids group. At follow-up, it showed comparable stable improvement at 3 and 37 months, but again displayed a small statistical difference in favor of patients with adenomyosis with fibroids at 7 years. This finding is concordant with a recent metaanalysis [12], but could also be explained by the initial selection bias were patients with pure adenomyosis had worse symptoms compared to the patients with adenomyosis and fibroids. The majority of patients (72%) declared to be at least fairly satisfied about UAE, however one-third of patients was either not satisfied or indecisive. Menopause was reported by 42% of patients and did not reveal any differences between patients with adenomyosis and patient with adenomyosis and fibroids. We recognized that the age and subsequently menopause could bias the result in terms of high HRQOL and decreased SSS. Improvement not as result of UAE, but as a result of menopause and the absence of menstrual cycle related symptoms. However, since these women at baseline had no other treatment option than a hysterectomy when conservative management failed, a hysterectomy could be avoided in many of these patients. Therefore, we believe that embolization at the very least postponed the recurrence of symptoms and avoided major surgery in many women. The median age of our population was 50 (range 36–59). In developed countries, the average age of women for reaching menopause is 51 years [17].

STRENGTHS AND LIMITATIONS

This is the longest follow-up cohort available so far. Other articles have reported long-term follow-up at 37, 40, 46, 48 and 58.8 months [7, 9, 13, 16, 18]. The cohort is relatively small which makes strong conclusions hazardous. As reported earlier [15], there was no difference between patients with pure adenomyosis and patients with adenomyosis and fibroids. Unfortunately, these groups are heterogeneous in terms of adenomyosis and fibroids size, location and dominance; therefore, strong conclusions aboutwhat type of adenomyosis responds best to UAE may not be drawn.

CONCLUSION

We conclude that after 7 years of follow-up, in 82% of patients UAE results in preservation of the uterus. Total of 72% of patients are at least fairly satisfied and 74% seem to respond well to UAE in terms of improvement of HRQOL and SSS.

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6

Uterine Artery Embolization for the Treatment of Adenomyosis: A Systematic Review and Meta-Analysis

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ABSTRACT

PURPOSE

The purpose of this systematic review and meta-analysis was to evaluate the effect of uterine artery embolization (UAE) on symptomatic adenomyosis.

MATERIALS AND METHODS

Four groups were evaluated: short-term (< 12 months) pure adenomyosis, short-term adenomyosis with fibroids (combined adenomyosis), long-term (> 12 months) pure adenomyosis, and long-term combined adenomyosis.

RESULTS

Improvement of symptoms occurred in 83.1% (872/1,049) of patients. Reported symptom reduction was 4.8% greater in the short-term combined group (P =0 .169) and 11.4% greater in the long-term combined group (P = 0.003). Uterine volume was reduced in all patients at 3 months.

CONCLUSION

The effects of UAE on symptom improvement and uterine volume reduction in patients with adenomyosis are encouraging.

INTRODUCTION

Adenomyosis refers to the benign presence of ectopic endometrial glands and stroma causing reactive hypertrophy of the smooth muscle fibers of the myometrium [1, 2]. Approximately one third of women with adenomyosis are symptomatic [3]. Diagnosis based on clinical findings is difficult because of the nonspecific array of symptoms (abnormal menstrual bleeding, pain, and bulk-related symptoms) and coexistence with other benign pelvic diseases (leiomyoma, endometriosis) [4, 5] Until recently, the diagnosis of adenomyosis depended on histology following invasive surgery; therefore, its incidence and prevalence have not been accurately established [6] Nowadays, the consistency of reporting based on transvaginal ultrasound and magnetic resonance (MR) imaging has been better established, and there are increasing data regarding the correlation of imaging to histology. Among conservative therapies, the levonorgestrel intrauterine system is shown to be effective in patients with symptomatic adenomyosis [7], however, if conservative treatment fails, no treatment options remain other than hysterectomy. For these reasons, alternative treatments, such as uterine artery embolization (UAE), need to be explored. Positive results reported by randomized controlled trials in the treatment of uterine fibroids [8-10] led to multiple case series during the last 18 years investigating UAE as a possible treatment option for patients with symptomatic adenomyosis [11-23]. The purpose of this systematic review and meta-analysis was to summarize and evaluate the effect of UAE on symptomatic pure adenomyosis and adenomyosis combined with fibroids in terms of symptom improvement and MR imaging outcomes.

METHODS

This systematic review was conducted and reported in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [24]. The methods
were specified in advance and registered in the PROSPERO International prospective register of systematic reviews [25]. The full literature search is described in appendix 1.

TYPE OF STUDIES, PARTICIPANTS, INTERVENTIONS, AND OUTCOMES MEASURES.

Both controlled and noncontrolled studies were included. Articles in all languages were included. Chinese, French, and German studies were translated by native speakers. Inclusion criteria were as follows: (i) patients age ≥ 18 years,

(ii) patients with symptomatic pure adenomyosis or adenomyosis in combination with fibroids (combined adenomyosis), and (iii) patients undergoing UAE. UAE was performed with the following agents: polyvinyl alcohol (Contour; Boston Scientific, Marlborough, Massachusetts) particles, trisacryl gelatin microspheres (EmboSphere; Merit Medical Systems, Inc, South Jordan, Utah), hydrogel microspheres (Embozene; Boston Scientific), sodium alginate microspheres (manufacturer not reported), gelatin sponge pledgets (Gelfoam; Pfizer Inc, New York, New York), domestic iodized oil (Lipiodol; Shanghai Xudong Co, Ltd, Shanghai, China), and pingyangmycin Lipiodol emulsion (Shanghai Xudong Co, Ltd). The included studies reported on primary and secondary outcomes. Primary outcomes included improvement of clinical symptoms (abnormal and/ or heavy menstrual bleeding, pain and/or dysmenorrhea, and bulk-related symptoms) and secondary intervention rate. Symptom improvement was defined as less severe or fewer complaints compared with baseline. Secondary outcomes included imaging outcomes (uterine volume, junctional zone [JZ], and infarction rates) and clinical outcomes (fertility and complication rate).

STUDY SELECTION, DATA COLLECTION PROCESS, AND RISK OF BIAS.

Two reviewers (A.M.d.B., C.W. [for Chinese articles]) extracted the data based on the Cochrane Consumers and Communication Review Group data extraction template [26]. A third reviewer (M.S.) checked the extracted data. In case of disagreement about the inclusion or exclusion of studies, a fourth reviewer (W.J.K.H.) was consulted. The final decision was reached by consensus. The following data were extracted from each included study: (a) specific study characteristics (authors, year of publication, study design, number of participants, inclusion period, follow-up duration); (b) characteristics of the study participants (inclusion and exclusion criteria, type of adenomyosis, age, clinical symptoms); (c) type of intervention(UAE materials used, anesthesia), (d) imaging characteristics (type of imaging used, diagnostic criteria); and (e) primary outcome (improvement of clinical symptoms) and secondary outcome (decrease of uterine volume, decrease of JZ, infarction of adenomyosis, fertility, complications). Quality of reporting, risk of bias, confounding, power, and external validity were assessed using the Downs and Black scoring system [27]. Three reviewers (A.M.d.B., M.S., C.W. [for Chinese articles]) discussed the scored items until they reached consensus. The following 3 quality score classifications were defined: good (score 24–32), fair (score 14–23), and poor (< 14) (Table 1). Risk of publication bias was evaluated by means of a funnel plot (appendix 2).

ANALYSIS

Clinical Outcomes. Improvement of symptoms after UAE was analyzed by the χ^2 test on individual patient data. This resulted in analyses of 4 groups: short-term (< 12 months) pure adenomyosis, short-term combined adenomyosis, long-term (> 12 months) pure adenomyosis, and long-term combined adenomyosis. A sensitivity analysis of data extracted from studies with quality scores ≥ 14 in the Downs and Black scoring system was conducted to test the overall analysis outcome validity. Imaging Outcomes. A fixed model meta-analysis was performed on eligible data containing 3-month absolute uterine volume comparing pure adenomyosis and combined adenomyosis. Sensitivity analysis of imaging data from higher quality studies (score > 14) was not possible owing to limited imaging data. Percentage decrease in uterine volume was compared between pure and combined adenomyosis for every follow-up moment. P values < 0.05 were considered statistically significant.

RESULTS

STUDY SELECTION AND STUDY CHARACTERISTICS

The study selection process is displayed in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram in Figure 1. The trial register search identified 1 ongoing randomized controlled trial (QUESTA [QUality of life after Embolization vs. hySTerectomy in Adenomyosis]) [46]. The examination of studies resulted in inclusion of 30 observational trials and yielded follow-up data from 1,049 patients with adenomyosis (pure and combined) on improvement of symptoms and secondary hysterectomies. One study of the same research group was excluded because of a suspected overlap between patient populations from 2 studies published 2 years apart [47]. Table 1 depicts study characteristics of the included 22 prospective cohorts and 8 retrospective cohorts. There were no case-control or randomized controlled studies. Duration of follow-up was reported in all studies and ranged from 3 months [35] to 65 months [37] (mean follow-up duration of 23.7 months). The median sample size was 23 patients (range, 6–159 patients) per study. Studies were executed in 10 different countries: China (n = 9), Korea (n = 7), United States (n = 4), Netherlands (n = 3), Australia (n = 1), France (n = 1), Germany (n = 2), Canada (n = 1), and United Kingdom (n= 1).

PARTICIPANTS AND METHODOLOGICAL QUALITY OF INCLUDED STUDIES (TABLE 1)

All studies included women treated with UAE for symptomatic pure adenomyosis and/or combined adenomyosis (Table 1). Adenomyosis was identified with MR

imaging (JZ > 12 mm) in 1,036 patients. Two studies identified some patients with adenomyosis via ultrasound or endometrial biopsy (n = 13 patients) [21, 31]. Five studies [31, 33, 34, 37, 41] used the standardized Uterine Fibroid Symptom and Quality of Life (UFS-QOL) questionnaire to evaluate health-related quality of life (HRQOL) and symptom severity. None of the included studies described potential sources of bias and/or confounding; no studies reported data on patients lost to follow-up; some studies did not report on patient selection.

TABLE 1. Study characteristics

ID	Design	Period	*n*	Intervention: Uterine artery embolization material	Follow-up (mo)	Indication	Primary outcome	Secondary outcome	Quality score [1]
Goodwin 199 *[15]	Retro. cohort	NR	6	NR	10.2	AUB, dysmenorrhea	Improvement sympt.	NA	**16**
Siskin 2001 *[22]	Retro. cohort	NR	13	255-500 µm PVA	8.2	AUB, dysmenorrhea, Bulk	Improvement sympt., HRQOL	JZ thickness	**13**
Chen 2002 *[12]	Prosp. Cohort	1999-2000	23	GFP	16	AUB, dysmenorrhea	Improvement sympt.	uterine volume	**11**
Jha 2003 *[16]	Prosp. Cohort	1997-2001	9	500-700 µm PVA	12	AUB, dysmenorhea, bulk	Improvement sympt.	myometrial and JZ thickness	**11**
Toh 2003 *[23]	Retro. cohort	2000-2001	12	400-600 µm PVA	10.9	AUB, dysmenorrhea, Bulk	Improvement sympt.	uterine volume	**17**
Kim 2004 *[18]	Retro. cohort	1998-2002	43	250-710 µm PVA	3.5	AUB, dysmenorrhea, Bulk	Improvement sympt.	uterine volume, infarction	**13**
Pelage 2005 *[21]	Prosp. Cohort	1997-2002	10	355-500 µm PVA, 500-900 µm TGM	24	AUB, Bulk	Improvement sympt.	uterine volume	**17**
Chen 2006 *[13]	Prosp. Cohort	1994-2004	159	199-200 µm GFP, 300-500 µm PVA, 500-700 µm KMG	50	Dysmenorrhea	Improvement sympt.	NA	**10**
Kitamura 2006 *[19]	Prosp. Cohort	1999-2003	11	355-500 µm PVA, 500-700 µm TGM	12	AUB, dysmenorrhea, Bulk	Improvement sympt.	Uterine volume, JZ reduction	**15**
Kim 2007 *[17]	Prosp. Cohort	1998-2000	54	250-355 µm, 250-355 µm, 355-500 µm, 500-710 µm PVA	58.8	AUB, dysmenorrhea, Bulk	Improvement sympt.	Uterine volume, infarction	**12**
Lohle 2007 *[20]	Prosp. Cohort	2001-2004	29	500–700 um TGM, 700–900 um TGM	17	AUB, dysmenorrhea, Bulk	Improvement sympt.	Uterine volume, infarction	**18**
Zeng 2007 [28]	Prosp. Cohort	2000-2006	23	PLE	9	AUB, dysmenorrhea	Improvement sympt.	Uterine volume	**8**
Duan 2008 *[14]	Prosp. Cohort	2001-2004	23	500-700 µm KMG	60	AUB, dysmenorrhea	Improvement sympt.	Uterine volume	**13**
Liu 2008 [29]	Prosp. Cohort	NR	28	300-500 µm PVA, PLE	30	AUB, dymenorrhea	Improvement sympt.	Uterine volume	**6**

TABLE 1. Continued.

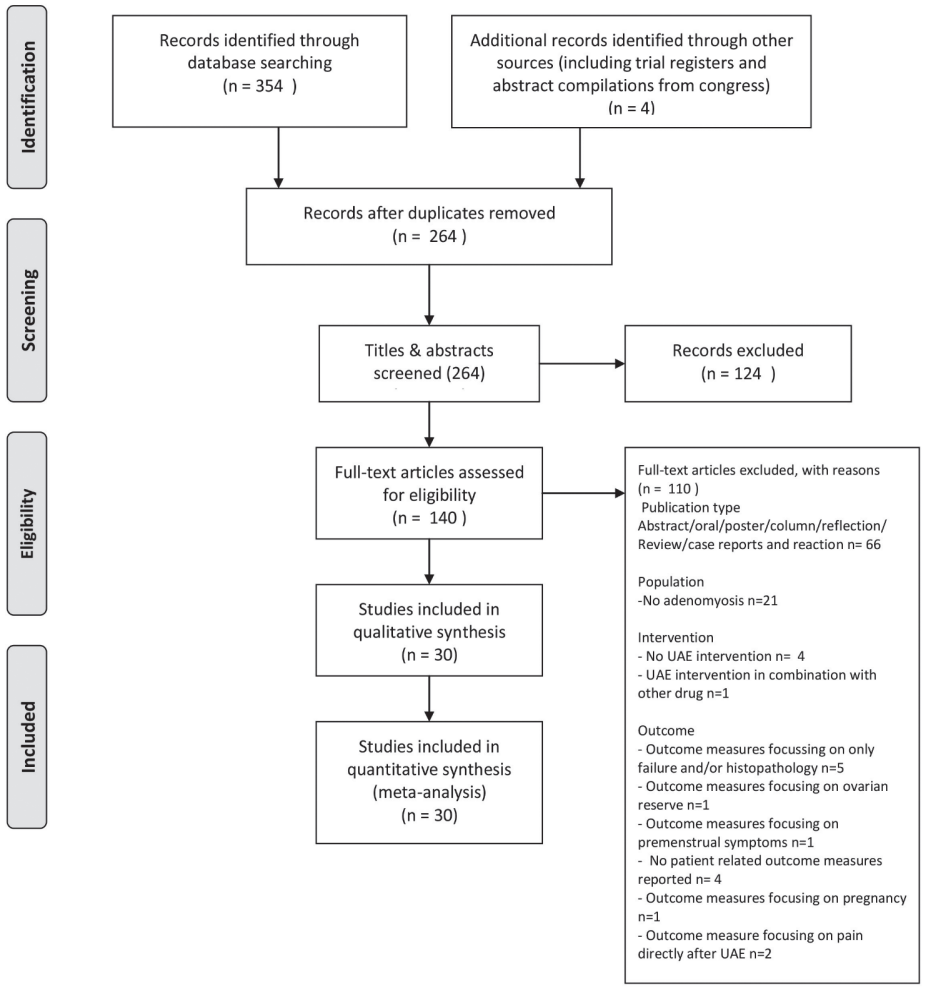
ID	Design	Period	*n*	Intervention: Uterine artery embolization material	Follow-up (mo)	Indication	Primary outcome	Secondary outcome	Quality score [1]
Bratby 2008 [11]	Prosp. Cohort	1998-2004	11	355–500 µm PVA	24	AUB, dysmenorrhea, Bulk	Improvement sympt.	Uterine volume	**12**
Ai 2010 [30]	Prosp. Cohort	2007-2008	80	500-700 µm KMG	12	Dysmenorrhea	Improvement sympt.	Uterine volume	**12**
Milo 2010 [31]	Prosp. Cohort	NR	7	300-500 µm PVA	6	AUB, dysmenorrhea, Bulk	Improvement sympt., UFS-QOL	NA	**15**
Kim 2011 [32]	Prosp. Cohort	2007-2009	21	1, 2, 3 protocol	14	AUB, dysmennorhea	Improvement sympt.	Uterine volume, infarction	**13**
Froeling Jan 2012 [33]	Retro. cohort	2002-2009	17	500-700 µm TGM	46	AUB, dysmenorrhea, Bulk	Improvement sympt., UFS-QOL	NA	**11**
Froeling June 2012 [34]	Prosp. Cohort	2001-2009	30	355-900 µm TGM	40	AUB, dysmenorrhea, Bulk	Improvement sympt. UFS-QOL	NA	**15**
Lee 2012 [35]	Retro. cohort	2008-2011	129	PVA, GFP	3	Overall symptoms	Imaging	Improvement sympt.	**12**
Liang 2012 [36]	Prosp. Cohort	2007-2010	17	300-900 µm PVA	24	AUB, dysmenorrhea, Bulk	Improvement sympt.	Satisfaction, uterine volume	**13**
Smeets 2012 [37]	Prosp. Cohort	1999-2006	40	500-700 µm TGM	65	AUB, dysmenorrhea, Bulk	Improvement sympt., UFS-QOL	Uterine volume, JZ thickness, infarction	**18**
Chang 2013 [38]	Retro. cohort	2008-2011	6	1, 2, 3 protocol	3	AUB, dysmenorrhea, Bulk	Imaging	NA	**18**
Yao 2013 [39]	Prosp. Cohort	2007-2012	15	300-500 µm PVA, 500-700 µmTGM	24	AUB, dysmennorhea	Improvement sympt.	Uterine volume	**12**
Bae 2015 [40]	Retro. cohort	2008-2012	50	1, 2, 3 protocol	48	Overall symptoms	Improvement sympt.	Uterine volume	**17**
Nijenhuis 2015 [41]	Prosp. Cohort	2006-2010	29	500-900 µm hydrogel microspheres	37	AUB, dysmenorrhea, Bulk	Improvement sympt., UFS-QOL	Uterine volume	**19**
Park 2015 [42]	Prosp. Cohort	2011-2012	25	1, 2, 3 protocol	3	AUB, dysmenorrhea, Bulk	Uterine volume	NA	**16**

TABLE 1. Continued.

ID	Design	Period	*n*	Intervention: Uterine artery embolization material	Follow-up (mo)	Indication	Primary outcome	Secondary outcome	Quality score [1]
Yao 2015[43]	Prosp. Cohort	2004-2015	45	Lipiodol, 350-700 µm KMG	29.6	AUB, dysmennorhea	Improvement sympt.	Uterine volume	**14**
Wang 2016 [44]	Prosp. Cohort	2012-2013	115	500-700 µm TGM	12	AUB, Dysmenorrhea	Improvement sympt.	Uterine volume, infarction	**17**

Note. -NA = not applicable, NR = not reported, AUB= abnormal uterine bleeding, 1, 2, 3 protocol = 150-250um -> 250-355um -> 355-500um PVA till stasis, TGM= trisacryl gelatin microspheres , KMG = sodium alginate microspheres, GFP = gelatin sponge pledgets, PLE = domestic iodized oil (lipiodol), UFS-QOL = Uterine Fibroid Symptom and Quality of Life questionnaire, HRQOL = health related quality of life, JZ= junctional zone.
Quality score: good (24-32) fair (14-23) poor (<14).
* Reported in Popovic et al 2011[45]

FIGURE 1. Flow chart of study selection for systematic reviews and meta-analysis (preferred Reporting Items for Systems Reviews and Meta-Analysis)



PURE ADENOMYOSIS <12 MONTHS FOLLOW-UP

Table 2 presents an overview of follow-up interval and secondary intervention rate in included studies per group. Nine studies reported on short-term results for pure adenomyosis and reported improvement of symptoms in 275 of 307 (89.6%) patients [15, 16, 18, 19, 22, 23, 28, 35, 44]. In this group, 2.6% (8 of 307) of patients with < 12 months of follow-up underwent secondary hysterectomy owing to endometritis (n = 1), hematometra (n = 1), persisting symptoms (n = 2), recurrent symptoms (n = 3), and persisting symptoms following unilateral UAE (n = 1)[11, 15, 21, 34]. Table 3 shows

the improvement in symptoms subdivided into abnormal uterine bleeding (AUB), dysmenorrhea, and bulk-related symptoms. For pure adenomyosis, 2 studies described overall improvement of symptoms [15, 16], 2 studies reported specific dysmenorrhea score improvement in 83.3%–93.9% after 11.4 months [23, 44], and 2 studies reported improvement of every individual symptom (AUB, dysmenorrhea, and bulk-related symptoms) and concluded that AUB and dysmenorrhea seem to respond equally well to UAE with scores of 94.7%–100% after 6.3 months [18, 28].

COMBINED ADENOMYOSIS <12 MONTHS FOLLOW-UP AND COMPARISON WITH PURE ADENOMYOSIS

As presented in Table 2, 6 studies reported on short-term results for combined adenomyosis and reported improvement of symptoms in 133 of 141 (94.3%) patients [16, 19, 22, 30, 31, 35]. In this group, 2 of 141 (1.4%) patients underwent hysterectomy owing to persisting symptoms. The short-term improvement rate between pure and combined adenomyosis groups did not show a statistically significant difference (P = 0.169; absolute risk ratio [ARR] 4.8%) (Fig 2). Sensitivity analysis of studies scoring ≥ 14 in the Downs and Black quality score showed comparable results within groups and did not reach a statistically significant difference between groups, supporting earlier findings (P = 0.290) (Fig 3) [15, 19, 23, 31, 44]. In Table 3, 5 of 6 studies reported on overall symptom improvement; however, only Milo et al [31] described all symptoms after scoring with the standardized UFS-QOL questionnaire. After a 6-month follow-up, all (7 of 7) patients with a baseline symptom severity score of 70 reported a symptom severity score decrease of 57.6 points. The remaining largest study with a high risk of bias described a very high improvement rate in 78 of 80 patients (97.5%) regarding only dysmenorrhea at 12 months of follow-up [30].

PURE ADENOMYOSIS >12 MONTHS FOLLOW-UP

As summarized in Table 2, 16 studies reported on long-term results for pure adenomyosis and reported improvement of symptoms in 318 of 430 (74.0%) patients [11-14, 17, 20, 21, 32-34, 36, 37, 39-41, 43]. In 31 of 430 (7.2%) patients, treatment failure resulted in a secondary hysterectomy in the long-term follow-up window. Table 3 shows the improvement of symptoms subdivided into AUB, dysmenorrhea, and bulk-related symptoms. Four studies reporting on AUB described improvement of symptoms in 81.3% of patients after a mean follow-up of 32.5 months [17, 21, 32, 43]. Four studies [14, 32, 39, 43] reported dysmenorrhea improvement rates of 78.6% after a mean follow-up of 31.9 months, and 2 studies reported bulk related symptoms to completely improve in 37.9% and partially improve in 47.8% of patients [17, 21].

Five of 16 studies described all individual symptoms: AUB, dysmenorrhea, and bulk-related symptoms in 88.8%, 89.3%, and 84.3% [20, 33, 34, 37, 41]. Three of these five studies additionally regarded health related quality of life. Froeling et al. [34] showed improvement in HRQOL scores, but reported lower scoring in the pure adenomyosis group compared with the combined group.

COMBINED ADENOMYOSIS >12 MONTHS FOLLOW-UP AND COMPARISON WITH PURE ADENOMYOSIS

Ten studies reported on long-term results for combined adenomyosis and demonstrated improvement of symptoms in 171 of 146 (85.4%) patients (Table 2) [11-13, 20, 29, 33, 34, 36, 37, 41]. In 12 of 146 (7.0%) patients, treatment failure resulted in a secondary hysterectomy in the long-term follow-up window. Figure 2 outlines a meta-analysis comparing improvement in the pure adenomyosis group with the combined adenomyosis group. The long-term combined adenomyosis group demonstrates a statistically significant improvement of symptoms compared with the long-term pure adenomyosis group (P =0.003; ARR 11.4%). Long-term sensitivity analysis supports earlier findings in favor of the combined adenomyosis group; however, the difference between the groups was smaller and no longer statistically significant (P = 0.107; ARR 3.7%) (Fig 3). Six studies in the long-term combined adenomyosis group did not report on individual symptoms (AUB, dysmenorrhea, and bulk-related symptoms) separately (Table 3) [11, 20, 33, 34, 37, 41]. Five of these studies used a standardized questionnaire [20, 33, 34, 37, 41]. Froeling et al [33] reported a statistically significant improvement of HRQOL in all 17 patients, including pure and combined adenomyosis, with a HRQOL score of 44.4 before UAE and 99.6 after UAE (P = 0.002).

TABLE 2. Follow-up interval and secondary intervention rate per group

Reference	pts	improved	follow-up (mo)	hysterectomy
Pure adenomyosis short term FU <12 months				
Goodwin 1999 [15] *	6	3	10.2	3 (**1,2**[1]**;4.2**[1];14 mo)
Siskin 2001 [22] *	6	6	8.2	0
Jha 2003 [16] *	3	3	12	0
Toh 2003 [23] *	12	10	10.9	0
Kim 2004 [18] *	43	40	3.5	0
Kitamura 2006 [19] *	7	6	12	0
Zeng 2007 [28]	23	22	9	0 (1x repeat UAE)
Lee 2012 [35]	92	77	3	NR
Wang 2016 [44]	115	108	12	0
Total	307	275 (89.6%)	9.0	2 +6[1] (2.6%)
95% CI		(86.1-93.2)		
Combined adenomyosis short term FU <12 months				
Siskin 2001[22] *	7	6	8.2	0
Jha 2003 [16] *	6	6	12	0
Kitamura 2001[19] *	4	4	12	0
Ai 2010 [30]	80	78	12	NR
Lee 2012 [35]	37	32	3	NR
Milo 2010 [31]	7	7	6	0
Total	141	133 (94.3 %)	8.9	0 + 2[1] (1.4%)
95% CI		(90.5-98.2)		
Pure adenomyosis long term FU >12 months				
Chen 2002 [12] *	19	18	16	0
Pelage 2005 [21] *	10	5	24	5 (**3.9**[1]**; 9**[1]**;** 13; 25; 27 mo)
Chen 2006 [13] *	117	92	50	9 (12-49 mo)
Kim 2007 [17] *	54	31	58.8	5 (NR)
Lohle 2007 [20] *	15	12	15	2 (NR)
Bratby 2008 [11] *	5	3	24	2 (**2**[1]**; 8**[1] mo)
Duan 2008 [14] *	23	19	60	2 (24; 30 mo)
Kim 2011[32]	21	15	14	NR
Froeling 2012 [33]	7	5	46	2 (NR)
Froeling jun 2012 [34]	11	6	40	5 (**6**[1]**; 9**[1]; 24; 44; 69 mo)
Liang 2012 [36]	6	5	24	0 (1x secondary UAE at 15 mo)
Smeets 2012 [37]	18	14	65	3 (NR)
Yao 2013 [39]	15	8	24	NR
Bae 2015 [40]	50	38	48	1 (18 mo)

Reference	pts	improved	follow-up (mo)	hysterectomy
Pure adenomyosis long term FU >12 months				
Nijenhuis 2015 [41]	14	12	37	1 (17 mo, 3x secondary UAE at 6, 7, 14 mo)
Yao 2015 [43]	45	35	29.6	NR
Total	430	318 (74.0 %)	36.0	31 (7.2 %)
95% CI		(69.8-78.1)		
Reference	**pts**	**improved**	**follow-up (mo)**	**hysterectomy**
Combined adenomyosis long term FU >12 months				
Chen 2002 [12]*	4	3	16	1
Chen 2006 [13] *	42	39	50	0
Lohle 2007 [20] *	14	12	17	2 (NR)
Liu 2008 [29] *	28	28	30	NR
Bratby 2008 [11] *	6	3	24	0
Froeling 2012 [33]	10	7	46	2 (NR)
Froeling June 2012 [34]	19	13	40	5 (4†; 7†; 26; 39; 40)
Liang 2012 [36]	11	11	24	0
Smeets 2012 [37]	22	15	65	4 (NR)
Nijenhuis 2015 [41]	15	15	37	0
Total	171	146 (85.4 %)	34.9	12 (7.0%)
95% CI		(80.0-90.7)		

*Note: CI = confidence interval; FU = follow-up; NR = not reported; UAE = uterine artery embolization.

*Reported in Popovic et al, 2011 (45).

†< 12 months secondary hysterectomy, but reported in long-term FU studies

TABLE 3. Improvement of individual symptoms

ID	*n*	Abnormal bleeding	Dysmenorrhea	Bulk related symptoms	Overall symptoms	Follow-up (months)
Short term Follow-up group						
Goodwin 1999 *[15]	6	NR	NR	NR	3 (50%)	10.2
Siskin 2001 *[22]	13	NR	NR	NR	12 (92.3%)	8.2
Jha 2003 *[16]	9	NR	NR	NA	9 (100%)	12
Toh 2003 *[23]	12	NA	10/12 (83.3%; 3 compl; 2part)	NA	10 (83.3%)	10.9
Kim 2004 *[18]	43	38/40 (95%)	40/42 (95.2%)	25/32 (78.1%)	40 (95.2%)	3.5
Kitamura 2006 *[19]	11	NR	NR	NR	10 (90.9%)	12
Zeng 2007 [28]	23	14/14 (100%; 12 compl; 2 partial)	18/19 (94.7%, 17 compl; 2 partial)	2/2 (100% compl)	22(95.6%)	9
Ai 2010 [30]	80	NR	78/80 (97.5%)	NR	78 (97.5%)	12
Milo 2010 [31]	7	NA: symptom serverity score	NA: symptom serverity score	NA: symptom serverity score	7 (100%)	6
Lee 2012 [35]	129	NR	NR	NR	109 (84.5%)	3
Wang [44]	115	NA	108/115 (93,9%; 64 compl; 44 partial))	NA	108 (93,9%)	12
Total	448	52/54 (96,3%)	254/268 (91,1%)	27/34 (79,4%)	408/448 (91,1%)	8.9
Long term follow-up group						
Chen 2002 *[12]	23	21/23 (91.3%)	21/23 (91.3%; 19 compl; 2 part)	NA	21 (91.3%)	16
Pelage 2005 *[21]	10	5/9 (55.6%; 5 compl)	NA	3/6 (50%)	5 (50%)	24
Chen 2006 *[13]	159	NA	131/159 (82.4%;15 compl;9part)	NA	131 (82.4%)	50
Kim 2007 *[17]	54	27/42 (64.3%)	NR	19/23 (82.6; 8 compl; 11 partial)	31 (57.4%)	58.8
Lohle 2007 *[20]	29	24/24 (82.8%;15 compl; 9 part)	19/19 (100%; 13 compl; 6 part)	9/9 (100%; 6 compl; 3 part)	24 (82.8%)	17
Bratby 2008 [11]	11	6/11 (54.4%; 4 comp;2partial)	9/11 (81.2%; 4 compl; 5 partial)	9/11 (81.2%;4 compl; 5 partial)	6(54.4%)	24

TABLE 3. Continued

ID	n	Abnormal bleeding	Dysmenorrhea	Bulk related symptoms	Overall symptoms	Follow-up (months)
Long term follow-up group						
Duan 2008 *[14]	23	NR	19/23 (82.6%)	NA	19 (82.6%)	60
Liu 2008 [29]	28	28/28 (100%)	28/28 (100%)	NA	28 (100%)	30
Kim 2011 [18]	21	15/15 (100%)	13/15 (86.7%)	NR	15(71.4%)	14
Froeling Jan 2012[33]	17	NA: symptom serverity score	NA: symptom serverity score	NA: symptom serverity score	12 (70.6%)	46
Foeling June 2012[34]	30	NA: 33/36 (91.7%; 28 compl;5 part)	NA: 31/34 (91.2%; 23 compl; 8 part)	NA: 28/30 (93.3%; 22 compl; 6 part)	19 (63.3%)	40
Liang 212 [36]	17	14/15 (93.3)	6/7 (85.7%)	NR	16 (94.1%)	24
Smeets 012 [37]	40	30/38 (78.9%)	25/31 (80.6%)	22/31 (70.9%)	34 (82.9%)	65
Yao [39]	15	NR	8/15 (53,3%)	NR	8 (53,3%)	24
Bae [40]	50	NR	NR	NR	38 (76,0%)	48
Nijenhuis [41]	29	NA: symptom serverity score	NA: symptom serverity score	NA: symptom serverity score	27 (93,1%)	37
Yao [43]	45	43/45 (95,6%)	37/45 (82,2%)	NA	35 (77,8%)	29,6
Total	601	246/286 (86.0%)	347/410 (84,6%)	90/110 (82,7%)	469/602 (77,9%)	35.7
Short and long term individual symptom score						
Total of all	1049	298/340 (87.8%)	601/678 (88.7%)	117/144 (81.3%)	877/1050 (83.6%)	23.74
95% CI		(84.3-91.3)	(86.1-91.1)	(74.8-87.7)	(81.3-85.8)	

*Note: –ND = not able to dived groups into pure or combined adenomyosis. NA = not applicable, NR = not reported.
* Reported in Popovic et al 2011[45]

FIGURE 2. Improvement of clinical symptoms (%)

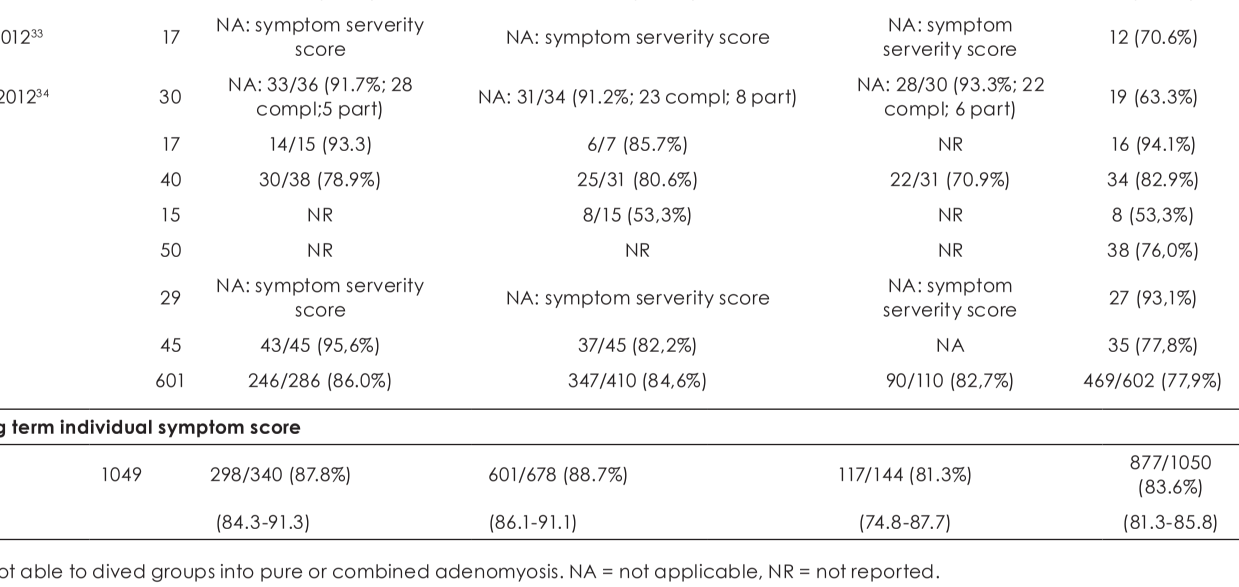
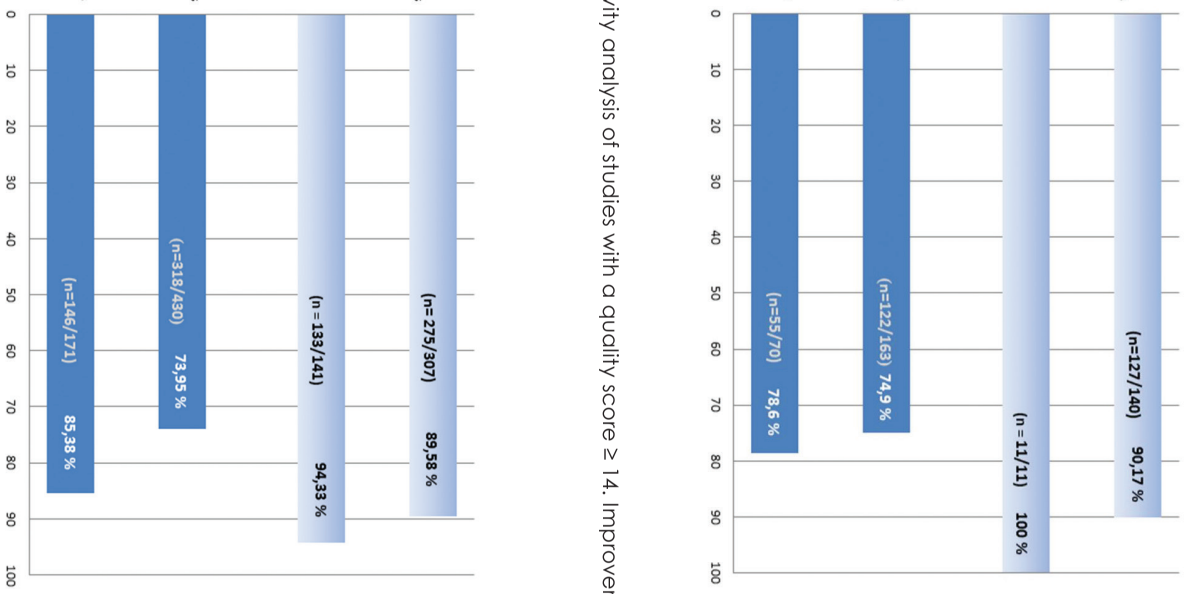


FIGURE 3. Sensitivity analysis of studies with a quality score ≥ 14. Improvement of clinical symptoms (%).



PREGNANCY OUTCOMES

Two of 34 studies reported fertility outcomes in terms of pregnancy after UAE. Kim et al[17] reported on 5 pregnancies reported on 5 pregnancies. Two of these patients underwent elective abortion owing to unwanted pregnancies. The remaining 3 patients carried to term and showed no signs of uteroplacental vascular insufficiency or abnormal uterine contraction during labor or postpartum. The pregnancies resulted in 2 vaginal deliveries and 1 elective cesarean delivery because of previous cesarean delivery. The average weight of neonates was 3.2 kg (range, 3.1–3.4 kg). Yao et al [43] described 1 pregnancy after UAE reporting termination of the pregnancy after 26 weeks. The reason for termination was not reported. Of 99 patients, 6 (6%) became pregnant after UAE.

COMPLICATIONS

There were 20 studies that reported on complications in 615 Patients [12, 14, 19-23, 28-30, 32-34, 36, 37, 39-41, 43, 44]. Abdominal pain occurring directly following the procedure until 2 weeks after the procedure was described in 361 of 413 patients (87.4%) [12, 14, 21, 22, 28-30, 32, 36, 39, 43, 44]. Persistent amenorrhea was reported in 28 of 445 patients (6.3%) in 13 studies. All of these patients were > 40 years of age [11, 17, 18, 20-23, 32, 36, 37, 40, 41, 44]. Nijenhuis et al [41] and Bae et al [40] reported a pseudoaneurysm, which was treated with a thrombin injection. Spontaneous expulsion of leiomyomata was reported in 10 patients [12, 20, 23]. Endometritis was suspected in 4 patients. These patient were treated with broad-spectrum antibiotics. Deep venous thrombosis of the calf occurred in 1 patient; however, this patient did not require anticoagulation therapy [15, 36]. No deaths or other complications occurred.

IMAGING OUTCOMES: UTERINE VOLUME

An overview of imaging outcomes is presented in Table 4 [11, 12, 14, 17-21, 23, 29-32, 38, 40-44]. Imaging follow-up was performed in 581 patients between 3 and 24 months after UAE. The studies are allocated to the time frame in which the imaging was conducted and divided into the 2 groups of pure adenomyosis and combined adenomyosis. Table 5 displays absolute uterine volume. Based on our meta-analysis, the weighted mean reduction of absolute uterine volume at 3 months compared with baseline was statistically significantly greater in the pure adenomyosis group than in the combined group [14, 18, 19, 30, 32, 38, 42] Figure 4 demonstrates percentage decrease in uterine volume between pure and combined adenomyosis for every follow-up point. At 3 months, a statistically significant difference in uterine volume percentage decrease was found between the pure adenomyosis group and the combined adenomyosis group

($P < 0.01$) [14, 17-19, 21, 23, 29, 32, 38, 40-44] Uterine volume percentage decrease was similar in the 2 groups at 6 months ($P = 0.94$) and 12 months ($P = 0.93$). Longer follow-up data on uterine volume percentage decrease in the combined adenomyosis group are not available owing to limited data reporting. Our results show a plateau phase after 12 months in the pure adenomyosis group.

TABLE 4. Imaging outcomes

ID	*n*	MRI criteria	Follow-up (mo)	Uterine reduction (mean %)	Junctional zone reduction (mean %)	Infarction rate (%)
3 month follow-up: pure adenomyosis						
Kim 2004 * [18]	43	JZ>12mm	3.5	32.5	NR	44.2 (complete n=19, Focal) 27.9 (parial n=12) 25.6 (no infarction, n=11)
Kitamura 2006 * [19]	11	JZ>12mm	3.5 (0.2-5.0)	35.24	15[1]	NR
Kim 2007 * [17]	22	JZ>12mm	3.3 (SD 1.8)	26.3	NR	65.2 (complete, focal) 68.8 (partial. Diffuse)
Duan 2008 * [14]	40	NR	3	16.0	NR	NR
Kim Aril 2011 [32]	40	JZ>12mm	3	43.2	NR	82.5 (complete, n=33) 5 (partial, n=1) 12.5 (no infarction, n=5)
Chang 2013 [38]	2	NR	3	52.0	NR	76.7 (complete, n=69) 21 (partial, n=21)
Bae 2015 [40]	50	JZ>12mm	3	49.1	NR	NR
Nijenhuis 2015 [41]	14	JZ>12mm	3	25.0	38.0	NR
Wang 2016 [44]	115	NR	3	28.0	NR	NR
Total	**337**					

TABLE 4. Continued

3 months follow-up: combined adenomyosis						
Kitamura 2006 * [19]	4	JZ>12mm	3.5 (0.2-5.0)	30.45	13.7[1]	NR
Chang 2013 [38]	4	NR	3	37.0	NR	NR
Ai 2010 [30]	80	NR	3	8.0	NR	NR
Milo 2010 [31]	7	Sonography	3	37.8	NR	NR
Park 2015 [42]	9	JZ>12mm	3	45.4	NR	66.7% (complete, n=6 focal)
Park 2015 [42]	16	JZ>12mm	3	55.3	NR	81.2% (complete, n=13, diffuse)
Total	**120**					
6 months follow-up: pure adenomyosis						
Toh 2003 * [23]	12	NR	6	42.0	NR	NR
Pelage 2005 * [21]	16	JZ>12 (n=6 sonography)	5.3 (SD1.8)	15.0	NR	NR
Duan 2008 * [14]	40	NR	6	28.0	NR	NR
Yao 2015 [43]	45	JZ>12mm	6	30.0	NR	NR
Wang 2016 [44]	115	NR	6	37.0	NR	NR
Total	**247**					
6 months follow-up: combined adenomyosis						
Liu 2008 [29]	14	NR	6	41.83	NR	NR
Liu 2008 [29]	14	NR	6	43.59	NR	NR
Ai 2010 [30]	80	NR	6	28.0	NR	NR
Milo 2010 [31]	7	Sonography	6	41.4	NR	NR
Total	**115**					

TABLE 4. Continued

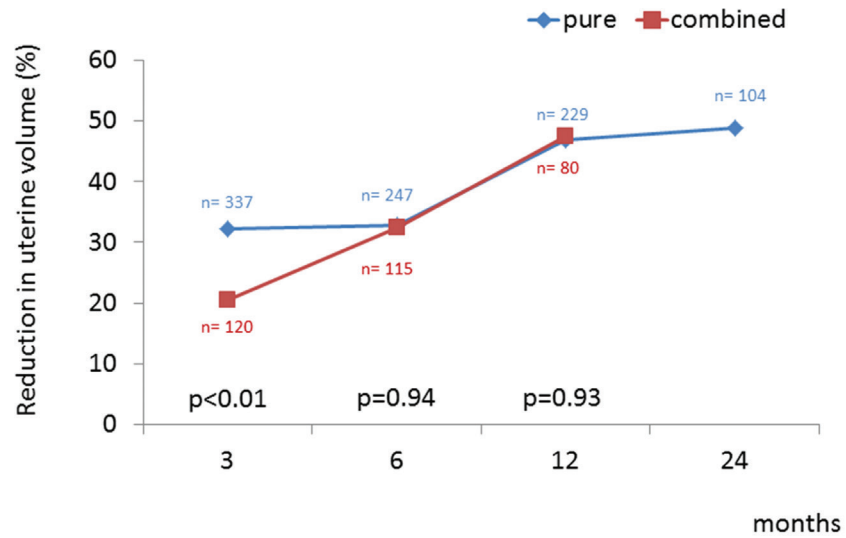
ID	*n*	MRI criteria	Follow-up (mo)	Uterine reduction (mean %)	Junctional zone reduction (mean %)	Infarction rate (%)
12 months follow-up: pure adenomyosis						
Lohle 2007 * [20]	12	JZ>12	12 (3-36 mo)	46.1	23,9[1]	44.2 * (90% median infarction)
Duan 2007 * [14]	40	NR	12	46.0	NR	NR
Yao 2015 [43]	45	JZ>12mm	12	50.0	NR	NR
Wang 2016 [44]	115	NR	12	51.0	NR	NR
Total	**229**					
12 month follow-up: combined adenomyosis						
Ai 2010 [30]	80	NR	12	38	NR	NR
Bratby 2009 * [11]	14	JZ>11	9 (2-12mo)	51	NR	NR
24 month follow-up: pure adenomyosis						
Chen 2002 * [12]	19	NR	24	37.0	NR	NR
Duan 2008 * [14]	40	NR	24	46.0	NR	NR
Yao 2015 [43]	45	JZ>12mm	24	54.0	NR	NR
Total	**104**					

Note NR= not reported [1] % reduction of all patients in this study.
* Reported in Popovic et al 2011 [45]

TABLE 5. Absolute uterine volume decrease at 3 months following UAE

ID	Baseline uterine volume	Decrease	95% Conf. Interval	
Pure adenomyosis				
Kim 2004 [18]	321,70	105.00	64.201	145.799
Kitamura 2006 [19]	307,52	150.34	-38.100	338.780
Duan 2008 [14]	252.00	40.00	27.604	52.396
Kim 2011 [32]	347,2	150.00	102.678	197.322
Chang 2013 [38]	788,55	83.20	53.823	112.576
Weighted overall effect		56.168	45.472	66.863
Combined adenomyosis				
Kitamura 2006 [19]	454,92	138.05	-220.601	496.701
Ai 2010 [30]	211.00	16.00	-6.119	38.133
Chang 2013 [38]	768,85	279.75	13.886	545.614
Park 2015 [42]	346,50	172.50	-112.223	457.223
Park 2015 [42]	342,10	183.80	86.119	281.482
Weighted overall effect		27.097	5.682	48.512

FIGURE 4. Uterine volumes prcentage decrease of pure and combined adenomyosis groups at 3-24 months of follow-up



IMAGING OUTCOMES: JZ AND INFARCTION

Six studies described a JZ reduction of 13.7%–38% (Table 4) [16, 19, 20, 22, 37, 41]. Smeets et al [37] reported a thicker JZ at baseline to be a possible predictor of UAE failure in patients with adenomyosis. Patients who underwent hysterectomy owing to persisting symptoms compared with patients with clinical improvement showed a statistically significant thicker JZ at baseline (P = 0.028) and during 3 months (P = 0.034) of follow-up. Another study by Nijenhuis et al [41] reported the mean JZ thickness at baseline not to be significantly thicker in groups with insufficient response (P = 0.17); however, it was statistically significant thicker in 4 patients needing additional therapy (P = 0.004). Adenomyosis infarction after UAE with rates ranging from 44.2% to 82.5% was reported in 7 studies [16-18, 20, 32, 40, 42]. Bae et al [40] reported an infarction cutoff analysis in which they concluded that patients with MR imaging infarction rate of < 34.4% had a 7 times higher risk of symptom recurrence (P = 0.001). Kim et al [32] reported that 4 of 5 (80%) patients without infarction had recurrence of symptoms compared with 2 of 16 (12.5%) patients with complete necrosis. One study reported no statistically significant correlation between improvement of symptoms and imaging at 3 months of follow-up [16].

DISCUSSION

SUMMARY OF FINDINGS

UAE for both pure and combined adenomyosis resulted in significant short-term and long-term symptom improvement. Hysterectomy rate in the short-term group varied from 2.6% in the pure adenomyosis group and 1.4% in the combined group. The long-term group showed a comparable hysterectomy rate of 7.2% in the pure adenomyosis group compared with 7.0% in the combined group. As a result, the total percentage of patients in the > 12 months group who underwent hysterectomy is 14.2% compared with 4% in the < 12 months group. When comparing groups, a statistically significant difference was calculated concerning improvement of symptoms in favor of the combined > 12 months group. In contrast to the overall improvement of symptoms analysis, the sensitivity analysis on data from studies with a quality score ≥14 did not show statistically significant improvement of symptoms between pure and combined adenomyosis in the > 12 months group. This might be explained by insufficient power (fewer studies). The weighted absolute uterine volume reduction at 3 months was statically greater in the pure adenomyosis group. Both thickened JZ at baseline and relatively low infarction rate of adenomyosis at 3 months may be predictive for therapy failure.

LIMITATIONS

Potential limitations of this systematic review and metaanalysis include the following: no randomized controlled trials were available, many included studies were retrospectively evaluated, many studies had a small sample size, and many studies offered vague description of methodology. Sample size of most included studies was not sufficient to draw solid conclusions, especially with respect to the uterine volume. Excluded patients and patients lost to follow-up were not reported by many studies, and therefore selection bias cannot be ruled out. Publication bias is most likely as supported by the funnel plots (appendix 2). Many individual studies did not report all information needed to properly weigh the quality of the study, which hampered this review. None of the studies included offered good quality evidence; 14 studies were scored "fair," and 16 studies were scored "poor." Other limitations consisted of heterogeneity in study outcomes. There were few validated questionnaires and instruments for symptom outcomes, and clear definitions of the primary outcome, secondary outcome, clinical success, and MR imaging diagnostic criteria for adenomyosis were lacking. Ideally, as long as adenomyosis-specific questionnaires are not available, the standardized UFSQOL questionnaire should be used in all future studies to have congruous and comparable outcomes [48]. MR imaging was often reviewed by multiple, but not independent, radiologists, and this could result in bias. Different embolic materials were used; the most widely used embolic agent was 255–900 μm polyvinyl alcohol particles. Standardized use of UAE particles in the treatment of adenomyosis is not available. Furthermore, longterm outcomes concerning fertility were described in only 2 of 30 studies. There were no studies comparing other treatments.

COMPARISON WITH OTHER STUDIES

One previously published review also reported improvement of symptoms after UAE in 75.5% (387 of 511) of patients with adenomyosis [45]. This review included 15 studies and concluded "the results being promising, but insufficient to establish embolization as a potential first line treatment of adenomyosis" [45]. The authors did not perform a systematic literature search or meta-analysis and performed only a limited qualitative assessment. Given the methodologic shortcomings of included studies, with the current evidence, drawing conclusions on clinical effectiveness following UAE should be avoided, and as a result the analysis and meta-analysis should be critically interpreted.

IMPLICATIONS FOR CLINICAL PRACTICE AND FUTURE RESEARCH

Symptoms resulting from adenomyosis can have a major impact on patients' quality of life and are an important health problem [49]. In the case of adenomyosis, concurrent benign gynecologic pathology is often present, increasing operative risks for major gynecologic surgery [4]. Furthermore, many women prefer uterus-preserving options [50]. An embolization is less invasive and generally requires a hospital stay of only 1 night. However, because the uterus is preserved, symptoms may continue (possibly to a lesser extent). If embolization proves to be comparable in terms of standardized measurements and definitions, this can be offered to patients as a less invasive alternative. This systematic review is valuable for clinicians dealing with patients who do not wish to undergo invasive surgery and are searching for an alternative treatment. Future trials should use standardized outcomes and validated questionnaires to render outcomes that can be extrapolated in systematic reviews. Also, future trials should focus on fertility results in patients with symptomatic adenomyosis.

CONCLUSION

UAE has favorable short-term and long-term outcomes whether it is performed for pure adenomyosis or adenomyosis in combination with fibroids. The included studies reported improvement of clinical symptoms in 83.1% (872 of 1,049) of patients. Greater JZ thickness (> 23 mm) and low infarction rates (< 34.4%) have been associated with decreased effectiveness for UAE in treating adenomyosis. Long-term follow-up (> 12 months) demonstrated less encouraging observations compared with the shortterm follow-up (< 12 months). Combined adenomyosis seems to respond better to UAE compared with pure adenomyosis in both the short-term and the long-term follow-up groups. Although this review does not support strong clinical conclusions regarding treatment, UAE seems to be a valuable treatment alternative to hysterectomy, although this needs to be confirmed in randomized controlled trials.

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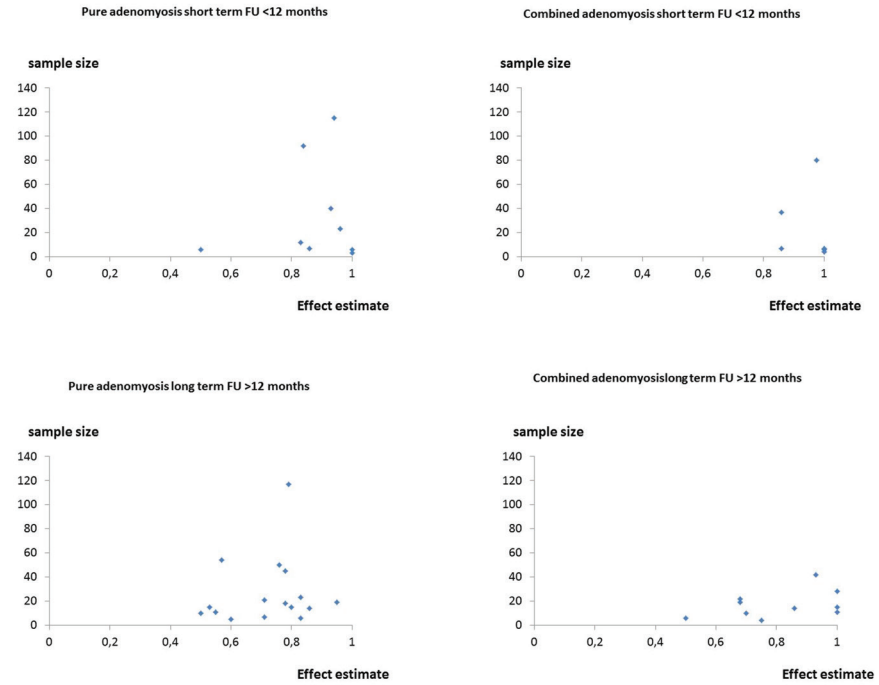
SUPPLEMENTARY MATERIALS

APPENDIX 1. INFORMATION SOURCE AND LITERATURE SEARCH

A comprehensive search was performed in the bibliographic databases PubMed and Embase from inception of the present study to September 16, 2016, in collaboration with a medical librarian. Search terms included controlled terms (MeSH in PubMed, Emtree in Embase) as well as free text terms. Search terms "adenomyosis," "endometrial adenoma," "endometriosis interna," "stromal endometriosis," "stroma endometriosis" were used in AND combined with search terms "embolization," "artificial embolism," "embolotherap*," "UAE." In addition, ClinicalTrials.gov (www. clinicaltrials.gov) and Nederlands Trial Register (www. trialregister.nl) were searched for not yet published or continuing studies. Reference lists of articles were crosschecked.

APPENDIX 2. funnel plots



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Uterine Artery Embolization Versus Hysterectomy in the Treatment of Symptomatic Adenomyosis: Protocol for the Randomized QUESTA Trial

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ABSTRACT

BACKGROUND

Adenomyosis is a benign uterine disease characterized by invasion of endometrium into the myometrium resulting in heavy menstrual bleeding and pain (dysmenorrhea). Hysterectomy is established as the final treatment option when conservative treatment fails. Uterine artery embolization (UAE) in patients with symptomatic adenomyosis has demonstrated to reduce symptoms and improve quality of life. However, randomized controlled trials are lacking.

OBJECTIVE

With this study, we aim to evaluate the impact of UAE on Health-Related Quality of Life (HRQOL) in a randomized comparison to hysterectomy in patients with symptomatic adenomyosis.

METHODS

This is a multicenter non-blinded randomized controlled trial comparing UAE and hysterectomy. Eligible patients are symptomatic premenopausal women without the desire to conceive and who have symptomatic magnetic resonance imaging (MRI)–confirmed pure adenomyosis or dominant adenomyosis accompanied by fibroids. After obtaining informed consent, patients will be randomly allocated to treatment in a 2:1 UAE versus hysterectomy ratio. The primary objective is HRQOL at 6 months following the assigned intervention. Secondary outcomes are technical results, pain management, clinical outcomes, HRQOL, and cost effectiveness during 2 years of follow-up. In addition, transvaginal ultrasound (TVUS) and MRI will be performed at regular intervals after UAE.

RESULTS

Patient enrollment started November 2015. The follow-up period will be completed two years after inclusion of the last patient. At the time of submission of this article, data cleaning and analyses have not yet started.

CONCLUSION

This trial will provide insight for caretakers and future patients about the effect of UAE compared to the gold standard hysterectomy in the treatment of symptomatic adenomyosis and is therefore expected to improve patients' wellbeing and quality of life.

TRIAL REGISTRATION

Netherlands Trial Register NTR5615; http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=5615 (Archived by WebCite at http://www.webcitation.org/6xZRyXeIF)

INTRODUCTION

Adenomyosis is described as the benign presence of ectopic endometrial glands and stroma causing reactive hypertrophy of the smooth muscle fibers of the myometrium [1, 2]. The prevalence of adenomyosis is estimated to be 5%-8% in some studies, whereas others find even 40%-70%[3-5]. Approximately one-third of women with adenomyosis are symptomatic [2]. Symptoms associated with the presence of adenomyosis are abnormal menstrual bleeding, pain (dysmenorrhea) and an enlarged uterus. About 40%-50% and 15%-30% of patients will suffer from heavy menstrual bleeding and/or dysmenorrhea, respectively [3]. Fibroids are present in up to 55% of the patients diagnosed with adenomyosis [6]. Therefore, it can be difficult attributing symptoms to one or the other [7, 8]. Adenomyosis can be diagnosed with transvaginal ultrasonography (TVUS) or magnetic resonance imaging (MRI)[9, 10] . Adenomyosis can be treated conservatively (hormonal/non-hormonal). When conservative management fails, a hysterectomy is the most common surgical solution, since surgical removal of adenomyosis is difficult given its diffuse aspect Uterine artery embolization (UAE) has been a minimally invasive treatment for symptomatic uterine fibroids since 1995 [11]. Since then, much research has been conducted including several randomized controlled trials establishing UAE as a valuable treatment option for women with symptomatic fibroids [12-14]. During the last fifteen years, several case series and cohorts evaluated UAE as a treatment for patients suffering from symptomatic adenomyosis. These cohorts show promising results [15-26]. Randomized data, comparing this new treatment modality with the gold standard (ie, hysterectomy) are lacking though. The "Quality of Life after Embolization vs Hysterectomy in Adenomyosis" (QUESTA) trial was set up to fill this knowledge gap comparing UAE with hysterectomy in patients with symptomatic adenomyosis. In this paper, we present the design of the trial.

METHODS

DESIGN

The QUESTA trial is a multicenter nonblinded randomized controlled trial, performed within selected hospitals in the Netherlands containing experienced interventional radiologists qualified to perform UAE. The study is performed in a network infrastructure in which radiologists and gynecologists collaborate. This trial will be conducted in accordance with the Consolidated Standard of Reporting Trials [27-29], the principles of the Declaration of Helsinki, and the Medical Research Involving Human Subject Act. This study is approved by the ethics committee of the VU Medical Centre Amsterdam (Reference Number 2015/211)

and by the boards of all participating hospitals. The trial is registered at the Netherlands Trial Registry (Netherlands Trial Register NTR5615).

PARTICIPANTS AND ELIGIBILITY CRITERIA

Eligible adult women are asked to participate when they meet the following inclusion criteria: 1. Premenopausal women with symptomatic pure adenomyosis or dominant adenomyosis (with concurrent uterine fibroids). Symptoms are defined as heavy menstrual bleeding, dysmenorrhea, and/or cycle independent pain and bulk-related symptoms. 2. Women with an indication for hysterectomy. These women had or have unsuccessful medicinal treatment or decided that such treatment is no option. The exclusion criteria are: 1. Patients younger than 18 years of age 2. Patients with a pelvic infection 3. Suspicion or presence of a malignancy 4. Current pregnancy or desire to conceive in the future 5. Absolute contraindication for angiography 6. Deep infiltrating endometriosis requiring surgery or risks on intestinal stenosis 7. Concurrent hysteroscopic removable submucous fibroids

PROCEDURES, RECRUITMENT AND RANDOMIZATION

When adenomyosis is suspected on TVUS (see criteria in Table 1) and MRI is performed to confirm adenomyosis (see criteria in Table 2), eligible patients will be informed about the study by the gynecologist, resident, research nurse or study coordinator and will be informed about the website for additional information and an introduction video (Multimedia Appendix 1). If the patient declines randomization, she will be asked to participate in the cohort group. The patients in the cohort study group will be offered standard care (ie, hysterectomy, since embolization is not available outside the trial). Afterwards, participants with written informed consent are randomly allocated (2:1) to the experimental intervention (UAE) or the standard care control group (hysterectomy). Randomization is computer-based and stratified for the participating hospitals. The study is not blinded since uterine artery embolization is performed either under conscious sedation or epidural anesthesia in contrast to a hysterectomy which is performed in the operating room under full narcosis. Therefore, it is not possible to blind the patients or the physicians.

TABLE 1. Criteria for diagnosing adenomyosis on TVUS

Criteria	eCRF answers
Uterus (cm)	Height*length*width
*Asymmetrical thickening	Yes/no/I don't know Measurements uterine walls
*Cysts	Yes/no/I don't know
*Fan-shaped shadowing	Yes/no/I don't know
*Myometrial aspect	Homogenous/inhomogeneous/I don't know
*Inhomogeneous endometrial-myometrial zone (endometrial lines/buds)	Yes/no/I don't know
*Diffuse flow	Yes/no/I don't know
Adenomyosis type	Diffuse Focal Combined diffuse > focal Combine focal > diffuse
Fibroids	Yes/no/I don't know
Fibroid count	Number
Size biggest fibroids (cm)	Height*length *width
Occurrence of pedunculated fibroid	Yes/no
Pedunculated fibroid count	Number

Note: *indicates adenomyosis criteria. If 3/6 are recognized adenomyosis is suspected.

TABLE 2. Criteria for diagnosing adenomyosis on MRI

Criteria and types	Definition	
Adenomyosis	# Junctional zone (JZ) >12mm diameter	
Cysts (hyper intense foci T2)	Yes/no	
Asymmetric myometria	Yes/no	
Adenomyosis category 1	Focal: 25% or less of endometrial interface	
Adenomyosis category 2	Regional: Entire endometrial surface of the anterior wall, posterior wall or fundus	
Adenomyosis category 3	Diffuse: Entire or most of the endometrial surface.	Superficial: <20mm Moderate: 20-29mm Severe: ≥ 30mm
Dominant adenomyosis in combination with fibroids	Volume domination: Adenomyosis> fibroids	

Note: # Adenomyosis is confirmed

INTERVENTION GROUP

A specific UAE particle protocol for adenomyosis will be delivered to the interventional radiologist of each center and, if needed, our experienced interventional radiologist will be present during the first UAE procedure (PNM Lohle). UAE is carried out under epidural anesthesia or patient controlled analgesia (PCA). A catheter is introduced in the femoral artery and positioned selectively into the uterine arteries under fluoroscopic guidance. Microspheres are then injected through the catheter into the uterine artery. The bloodstream will move the microspheres towards the small uterine artery branches in the area of adenomyosis (and fibroids if present). Microspheres consist of a hydrogel core with polymethylmethacrylate (PMMA) and a flexible shell of polyphosphazene (Polyzene-F), which is a synthesized inorganic biostable and biocompatible polymer (Embozene microsphere). This embolic agent establishes reduction and cessation of blood flow to the area of adenomyosis resulting in ischemia and infarction. The embolization protocol sets out the provisions regarding the microsphere size (Embozene 500 µm) for use and the angiographic embolization end-point until full stasis at the distal end of the uterine artery. A second protocol will include: administration of antibiotics, drip infusions, Foley bladder catheters, PCA pump usage with strict protocols for pain management, and a nursing protocol for the ward.

CONTROL GROUP

Hysterectomy is preferably performed by vaginal hysterectomy (VH) or total laparoscopic hysterectomy (TLH). A TLH or abdominal hysterectomy is always performed under general anesthesia. No protocol will be provided for surgical standardization. Adhesiolysis will be performed when necessary. Planned concomitant endometriosis surgery serves as an exclusion criterion. However, during surgery, coagulation of mild endometriosis is allowed. In case of laparoscopic or vaginal hysterectomy, the uterus will be removed vaginally or by the use of (in bag) morcellation. Supra cervical hysterectomy is allowed.

DATA COLLECTION

All electronic clinical report forms (eCRF) and patient questionnaires are digitally online secured and filled out in the study website with the use of a patient-specific study number [30]. The patient and physician receive this study number at time of informed consent. Figure 1 shows the study flowchart.

BASELINE

At time of inclusion and randomization, baseline medical history, obstetric history, and laboratory work up (hemoglobin, renal function (eGFR), CA-125, Anti-Mullerian hormone (AMH) in a subset of centers) are reported in the eCRF. The imaging characteristic displayed in Table 1 will all be registered. Patients will fill out validated Health-Related Quality of Life (HRQOL) and symptom questionnaires (see "outcome measures").

PROCEDURE

At procedure, data about the course of the intervention (UAE or operation), any particularities or complications are reported in the eCRF. At discharge from the hospital the eCRF will report the total of admitted days and complications during hospital stay.

FOLLOW-UP

The research investigator will send invitations for the digital online secured patient questionnaires by email at baseline, 6 weeks, 3 months, 6 months, 12 months and 24 months of follow-up. All patients will also specifically be asked at baseline to give their consent to be approached for long-term follow-up. Validated questionnaires will be filled out to report on HRQOL, symptoms, clinical outcomes, return to normal activities, absence of work, medication use, costs, medical consultation/consumption, and additional received therapy (see "outcome measures"). The patients who underwent UAE will receive a TVUS at 6 weeks and 6 months with an MRI at 6 months to compare the adenomyosis features with baseline results. In the hysterectomy group, pathology outcomes are also registered. All the eCRFs will report complications.

OUTCOMES MEASURES

The primary outcome is quality of life at 6, 12 and 24 months after index procedure as measured by a combination of the World Health Organization Quality of Life Scale (whoqol-Bref) and Short Form-12 (SF-12) Questionnaire. Secondary outcomes at 6 weeks and 3, 6, 12, 24 months after treatment consists of:

1. Clinical outcomes: technical failure rate, clinical failure rate as defined by secondary hysterectomy, additional therapy or reinterventions, complications.
2. Recovery related outcomes (6 weeks, 3 and 6 months): hospital stay, return to normal activities (Recovery Index-10).

3. Symptom and quality of life outcomes: menstrual characteristics (pictorial blood assessment chart), validated pain-questionnaire (Numeric Pain Rating Scale 0-100 scale, Facet 1: Pain and discomfort WHOQOL-100), sexual functioning (WHOQOL-100, sexual activity domain), satisfaction (Likert-scale, vignettes preference), quality of life (WHOQOL-Bref, SF-12).
4. Cost utility analysis (European Quality of Life 5 Dimensions) after 12 months.
5. Laboratory outcomes (baseline, 6 weeks and 6 months): hemoglobin, CA-125 and AMH in specific predefined centers.
6. Pathology outcomes (6 weeks): pathological finding of uterus in hysterectomy group.

Also, imaging outcomes will be investigated in order to identify potential predictive parameters for therapy effect.

1. TVUS (baseline, 6 weeks and 6 months): imaging parameters described in Table 1, uterine size reduction and reduction of fibroid volume in case of concomitant fibroids. In specific predefined centers, we will measure vascular index (3D power Doppler).
2. MRI (baseline and 6 months): imaging parameters described in Table 1, uterine size reduction, junctional zone reduction, infarction rate, reduction of fibroid volume in case of concomitant fibroids, presence of endometriosis.

SAMPLE SIZE

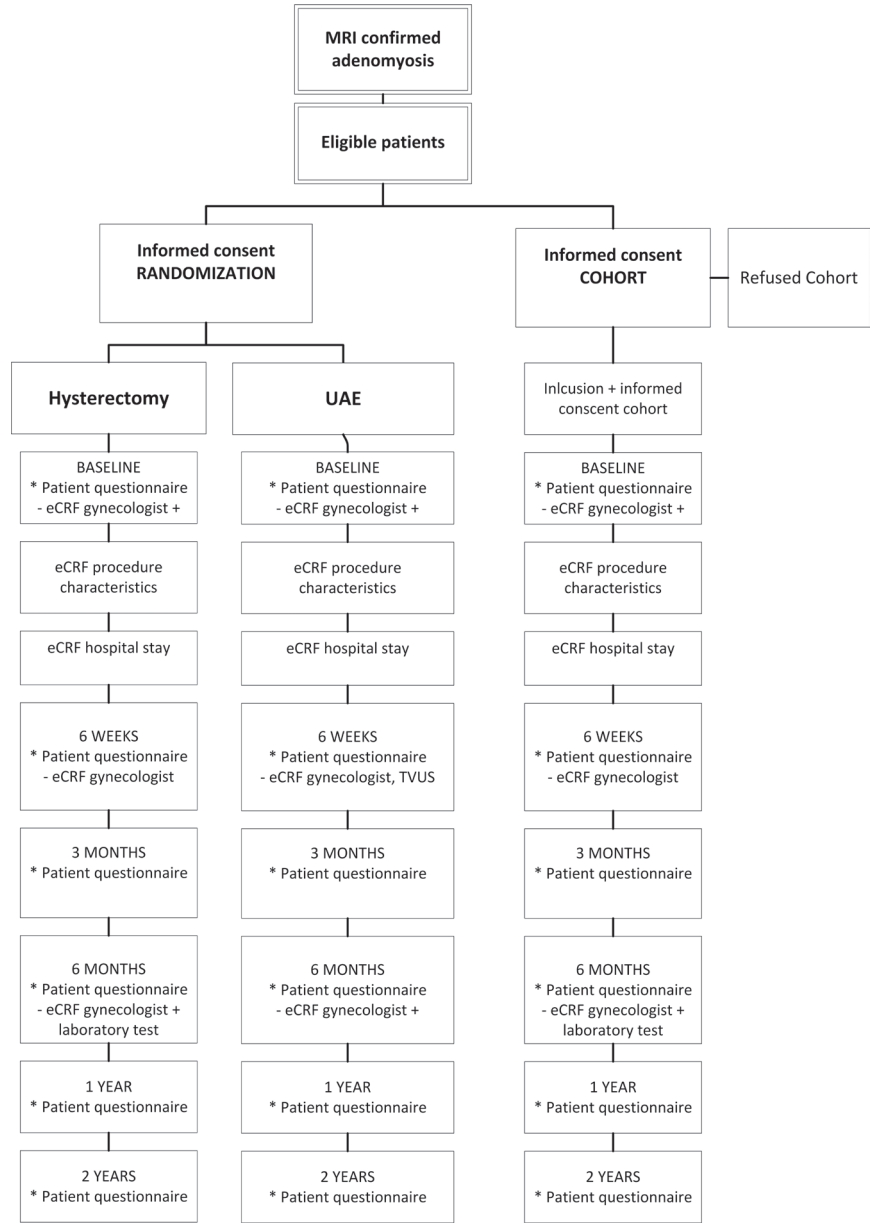
This study has a noninferiority design, where UAE is considered noninferior to hysterectomy when HRQOL at 6 months does not differ (delta) more than 5 points (scale 0-100). When the following assumptions are used: SD of 9 points (scale 0-100), alpha 0.10, power 0.80, using a one-sided two-sample equal-variance t test, a sample size of 1 x 52 patients (embolization) and 1 x 34 patients (hysterectomy) is needed. Excluding 10% dropout, in total 96 patients are needed for the primary outcome. Assumptions are based on the Embolization versus Hysterectomy (EMMY) trial outcomes [13].

STATISTICAL ANALYSIS

Analysis of the study will be based on the intention-to-treat and per protocol analysis. With regard to the primary outcome variable (WHOQOL-Bref, SF-12), non-inferiority is established between UAE and hysterectomy when the mean difference does not exceed 5 points (with a SD of 9 points). The primary outcome will be analyzed using linear mixed modeling, applying transformation if necessary, adjusting for, if necessary, clinically relevant baseline imbalances. With

regard to the secondary outcomes, we will use the appropriate nonparametric and parametric statistics to evaluate statistically significant differences between the two treatments. A P value <.05 will be considered as statistically significant. In all analyses, statistical uncertainties will be expressed in 90%CI. The database will be locked 6 months after the last surgical procedure in order to obtain the short-term outcomes. These data will be analyzed and published in a "short term results" manuscript. The long-term results (HRQOL and costs) will be analyzed 12 months after the last procedure, when the last patient returned her last questionnaire.

FIGURE 1. Study flowchart



Note: Patient data includes the following questionnaires: Pictorial Blood Assessment Chart (PBAC), Numeric Pain Rating Scale (NRS), Facet 1:Pain and discomfort WHOQOL-100, World Health Organization Quality Of Life-Bref (WHOQOL-Bref), Short Form-12 (SF-12), Facet 15: sexual activity domain WHOQOL-100, recovery (RI-10), Euro-QOL 5D (EQ-5D), patient preference (vignette), and patient satisfaction (Likert-scale).

SAFETY MONITORING AND INTERIM ANALYSIS

Since both treatment options have proven their safety, no specific risks apply. This study is conducted to determine the efficacy of the treatment. However, safety monitoring without direct involvement in the trial (clinical research bureau, VUMC) will be installed to monitor the setup and conduct of the trial. No interim analysis is planned because of the relatively small sample size. All serious adverse events (SAEs) will be reported to the accredited METC that approved the protocol, within 15 days after the sponsor has first knowledge of the serious adverse events. SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur no later than 48 days after the responsible investigator has first knowledge of the adverse event. In case of more than one SAE, the METC will be notified. This committee can advise to terminate the trial due to safety reasons.

RESULTS

Inclusion of patients started in November 2015. The expected end date is November 2019. Data collection for the primary outcome will be expected to last until May 2020. Data collection concerning the secondary outcomes are expected two years following the last included patient. Analysis has not yet started as of this article's submission.

DISCUSSION

SUMMARY

With this randomized controlled trial, we aim to evaluate the impact of UAE on HRQOL in a randomized comparison to hysterectomy in patients with symptomatic adenomyosis.

STRENGTHS AND LIMITATIONS

This is the first randomized controlled trial evaluating effectiveness of UAE versus hysterectomy in patients with symptomatic adenomyosis. The QUESTA trial uses a web-based randomization program with the use of allocation concealment which reduces the chance of selection bias. The study is not blinded for the patient or health care worker which could possibly influence the outcomes. Blinding is impossible considering the nature of the treatments. Earlier studies reported on UAE being more cost-effective compared to hysterectomy, however these studies were conducted in patients with fibroids and mostly carried out through abdominal hysterectomies [31]. Over the years hysterectomy techniques have changed and the more cost-effective laparoscopy has become available.

No studies have yet reported on cost effectiveness of UAE versus laparoscopic hysterectomy. We expect UAE to be more cost effective since the procedure itself is less expensive and recovery time is shorter [32], however we do expect consultation to be more frequent in the UAE group. We note that we allow all hysterectomy techniques in this study due to the intention to treat analysis. It will be registered and corrected for in analysis. Disease specific questionnaires for adenomyosis have not yet been developed. Used questionnaires are validated in terms of quality of life, pain, heavy menstrual bleeding, sexual functioning, recovery, and allocation satisfaction and proved to be disease specific in the EMMY trial [13]. The follow-up in this trial is set at 24 months. This could be a limitation since 5- and 10-year follow-up of the EMMY trial showed additional hysterectomies in the UAE group [33, 34]. Depending on the result of this trial a possibility to extend follow-up was included in the informed consent. In the last 15 years, 30 cohorts and case series [15-26, 35-52] described UAE in the treatment of symptomatic adenomyosis. The lack of level 1 evidence, heterogeneous particle use and UAE techniques make the development of a national guideline for standardized UAE in the treatment of adenomyosis challenging. We provide a mini-protocol on the usage of the standardized microspheres, however we do not provide a specific UAE technique protocol because we assume general UAE techniques will be followed [28]. In addition, we wish to maintain the intention to treat analysis of the Dutch population treated in the UAE centers.

POTENTIAL IMPACT AND IMPLICATIONS

Results of the QUESTA trial will provide knowledge for the most optimal treatment regimen in terms of HRQOL, side-effects, complications and satisfaction with allocated treatment. Hysterectomy requires hospitalization of 2 to 4 days, depending on the approach [31]. On the other hand, the source of adenomyosis is removed and might provide a more definite solution. An embolization is less invasive and in general, requires hospitalization of only 1 night [31]. Meanwhile, the uterus is preserved and complaints may continue (possibly to a lesser extent). How these pros and cons relate between the two strategies is unknown. If embolization proves to be comparable in terms of HRQOL, this can be offered to patients as a less invasive alternative, in particular in women that would like to preserve the uterus. These study outcomes could inform future patients about the expected effect of UAE and hysterectomy in the treatment of symptomatic adenomyosis and could therefore support shared decision making. These results are expected to improve patients' wellbeing and quality of life.

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SUPPLEMENTARY MATERIALS

APPENDIX 1. Text and animations on the website

8

A sonographic classification and reporting system for diagnosing adenomyosis

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ABSTRACT

OBJECTIVE

To develop a uniform classification and standardized reporting system of ultrasound findings of adenomyosis using the Morphological Uterus Sonographic Assessment (MUSA) criteria.

METHOD

The opinion presented in this manuscript was built based on a thorough discussion among all authors, including a Delphi procedure. Selected images and videos of typical cases of the different morphological variations of adenomyosis were used in the debates.

RESULTS

A classification and reporting system of different types of adenomyosis based on ultrasound was agreed upon including (1) identification of adenomyosis based on MUSA criteria, (2) disease location (anterior, posterior, left lateral, right lateral, fundal), (3) classification of the lesions as focal or diffuse, (4) presence or absence of intralesional cysts, (5) myometrial layer involvement (junctional zone, myometrium, serosal involvement), (6) disease extent (< 25%, 25- 50%, > 50% of uterine volume affected by adenomyosis) and (7) lesion size.

CONCLUSIONS

We proposes a uniform classification and reporting system of different types of adenomyosis based on ultrasound. The clinical relevance of this approach needs to be evaluated in further studies.

INTRODUCTION

In 2015 the international Morphological Uterus Sonographic Assessment (MUSA) group published a consensus paper on which terminology to use when describing myometrial lesions seen using ultrasonography [1]. The use of the MUSA terminology to describe ultrasound images of fibroids including their location according to the International Federation of Gynecology and Obstetrics (FIGO) is easy to implement [2, 3]. However, even though the MUSA-consensus statement suggests which terms should be used to describe ultrasound images of adenomyosis, it does not provide guidelines for how to classify morphological types or extent of adenomyosis [1]. We propose a uniform reporting system of ultrasound findings of adenomyosis. The opinion presented in this manuscript was built based on a thorough discussion among all authors, including a Delphi procedure (appendix 1). Selected images and videos of typical cases of the different morphological variations of adenomyosis were used in the debates.

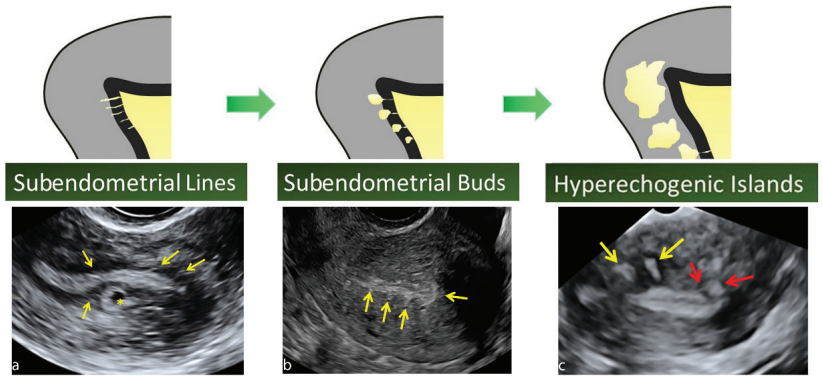
ULTRASONOGRAPHY AS A (SINGLE) DIAGNOSTIC TOOL

The gold standard for the diagnosis of adenomyosis is histological examination of a hysterectomy specimen. Because only a small and selected group of women undergo hysterectomy, an accurate estimation of the prevalence of the disease cannot be established [4]. The introduction of imaging techniques such as transvaginal ultrasonography (TVUS) and Magnetic Resonance Imaging (MRI), has allowed non-invasive diagnosis of adenomyosis [5-8]. Ultrasonography is widely available in an office setting, it is relatively inexpensive, requires no preparation, has no contraindications and is relatively accurate in experts hands, and is therefore the imaging modality of choice in gynecology [7]. Although adenomyosis is usually diagnosed in women between 40 and 60 years of age, it is also described in young women in whom any surgery performed on the uterus might adversely affect child-bearing [9]. Also in women over 40 years of age the treatment of choice for adenomyosis is primarily hormonal (e.g. levonorgestrel intrauterine device; oral progestins) [10]. Patient management is often based on an ultrasound diagnosis of adenomyosis only. This stresses the importance of a uniform, reproducible and clinically relevant reporting system of ultrasound findings compatible with adenomyosis. Uniform reporting also facilitates studies on the prevalence, etiology, and clinical implications of adenomyosis and on effectiveness of therapies.

PATHOGENESIS OF ADENOMYOSIS

There are different theories about the pathogenesis of adenomyosis. It is commonly thought that adenomyosis originates from direct contact between the endometrium and the underlying myometrium myometrium allowing for the formation of ectopic endometrial glands and stroma. Although there are multiple theories, the exact pathophysiological pathway is not known. Reported risk factors for adenomyosis include multiparity [11, 12] and previous uterine surgery [13-16] (curettage and cesarean delivery), suggesting a possible role of damage to the endometrial-myometrial junction. On the other hand, Kishi et al reported infiltration of endometriosis from outside the uterus where it disrupts the serosa and infiltrates the external myometrium inducing another subtype of adenomyosis [17]. Extrauterine adenomyosis has also been reported, e.g. in the rectovaginal septum [18]. Other theories are in-folding of endometrium which then penetrates into the myometrium, basement membrane damage through single nucleotide polymorphisms, initiation/progression of adenomyosis modulated by vascular factors and estrogen receptors [18-20]. Endometrial and myometrial damage allowing the growth of ectopic endometrial glands and stroma into the myometrium may explain ultrasound findings of sub-endometrial lines and buds with expansion to hyper-echogenic islands in the myometrium (figure 1) [1].

FIGURE 1. Ultrasound findings compatible with growth of endometrium into the myometrium



Note: a. Subendometrial lines: Tiny echogenic lines (yellow arrows); some tiny echogenic lines cross the JZ and are in contact with a small myometrial cyst with a typical echogenic rim (*)
b. Subendometrial buds: Echogenic lines/buds (yellow arrows) crossing the JZ
c. Echogenic islands: (yellow arrows), some with a hypoechogenic halo. Tiny echogenic line in contact with an echogenic bud/island (red arrows)

HISTOLOGY OF ADENOMYOSIS

Histologic diagnosis of adenomyosis is made by observing the presence of endometrial stroma and glands in the myometrium. Various histo-pathological definitions of adenomyosis have been reported but there is no consensus among pathologists: 1) disruption of the normal boundary between the endometrium and myometrium, 2) the ectopic endometrium is basal-type non-secretory tissue with a direct connection to the basalis layer, 3) myometrial invasion of endometrium >4 mm below the basalis layer 4) myometrial invasion of endometrium >2.5mm below the basalis layer, 5) >25% of the thickness of the uterine musculature as measured from the endometrial-myometrial junction is invaded by endometrium [5, 18, 21-23]. On histology adenomyosis is classified as focal if there are circumscribed nodular aggregates of endometrial glands and stroma surrounded by normal myometrium, while diffuse adenomyosis is described as diffusely distributed endometrial glands and stroma throughout the myometrium [24]. Adenomyomas are a subgroup of focal adenomyosis surrounded by hypertrophic myometrium [25]. Different histological disease severity classifications have been suggested but without international consensus [17, 26-30]. Ultrasound characteristics reflect histological features. Different morphological types of adenomyosis, seen at ultrasound examination or at histological examination, may reflect different stages in the development of the disease, or may have different clinical significance as to symptomatology, fertility, obstetrical outcome and therapeutic options. This underlines the need for an internationally accepted uniform classification of adenomyosis that preferably can be made by using ultrasound.

REPORTING ADENOMYOSIS

Following items should be assessed when examining and describing a uterus with adenomyosis (Table 1):

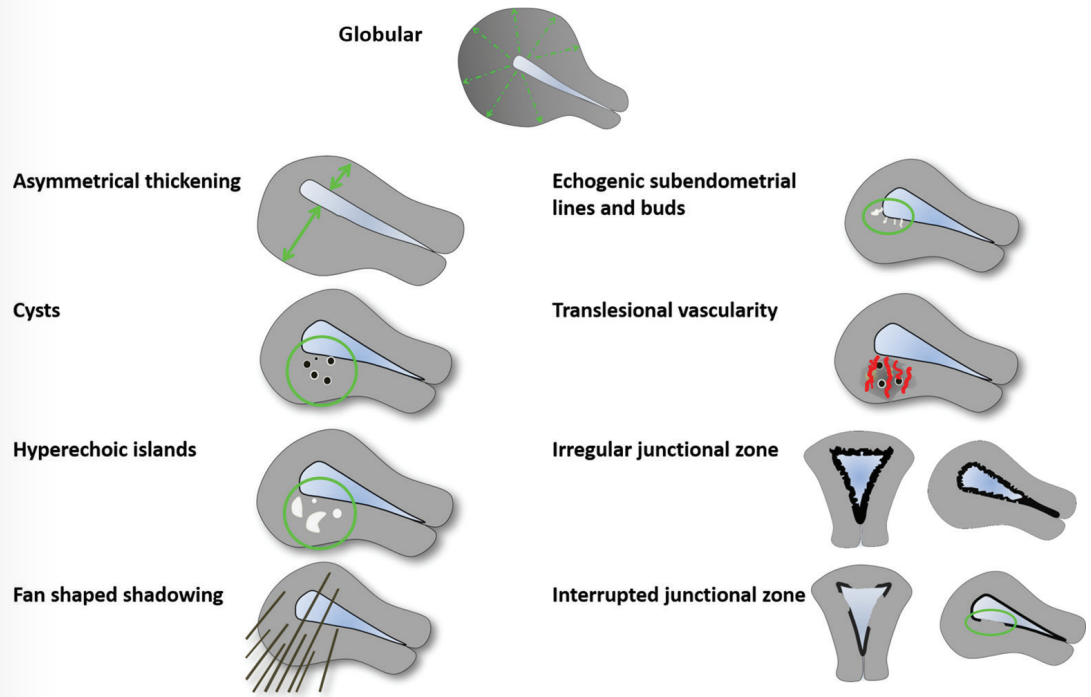
1) The myometrium needs to be classified as normal or as manifesting signs of adenomyosis, myoma, or sarcoma, using the MUSA terminology [1]. Other myometrial lesions to be considered in the differential diagnosis are accessory cavitated uterine masses (ACUM), also reported as juvenile cystic adenomyoma, and postoperative uterine scarring including focal loss of myometrium and fistulae [31]. The MUSA features typical of a uterus with adenomyosis include an enlarged globular uterus, asymmetrical thickening of the myometrium, myometrial cysts, echogenic subendometrial lines and buds, hyperechogenic islands, fan shaped shadowing, an irregular or interrupted junctional zone, and

translesional vascularity on color Doppler ultrasound examination (figure 2) [1]. The definitions of these features can be found in the MUSA consensus statement [1].

TABLE 1. Examples of the classification and description

Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	
Adenomyosis yes/no?	**Location**	**Classification (diffuse/focal)**	**Cystic**	**Layer involvement (type)**	**Extent**	**Size of the lesion (max. diameter)**	**Description**
Yes	Anterior wall	>25% of lesion surrounded by normal myometrium,	Yes	Sliding viscera: yes Junctional zone (inner myometrium) and middle myometrium (type 1-2)	< 25% of total myometrium	2 cm	**Focal type 1-2** cystic adenomyosis in the anterior wall. Extent: mild Diameter 2cm
Yes	Posterior wall	In doubt	Yes	Sliding viscera: no Junctional zone (inner myometrium), middle myometrium and outer myometrium (Subserosa) (type 1-3)	25-50% of total myometrium	3cm	**Diffuse type 1-3** cystic adenomyosis in the posterior wall. Extent: moderate Maximal diameter: 3cm
Yes	Anterior wall	<25% of total surrounded by normal myometrium	No	Junctional zone (inner myometrium) and middle myometrium (type 1-2)	>50% of total myometrium	7cm	**Diffuse type 1-2** adenomyosis in the anterior wall. Extent: severe Maximal diameter: 7cm
				Combinations			
Yes	Anterior wall	Adenomyoma	Yes	Type 1-2	Mild <25%	3cm	**Mixed type** cystic adenomyosis: type 1-2 adenomyoma in anterior wall and type 3 focal adenomyosis in left lateral side Extent: mild Maximal diameter: 1. Adenomyoma: 3 cm 2. Focal lesion: 2 cm
Yes	Left lateral wall	Focal	Yes	Type 3	Mild <25%	2cm	
Yes	Left lateral wall	Focal	Yes	Type 2	Mild <25%	4cm	**Mixed type** cystic adenomyosis: type 2 focal adenomyosis in left lateral wall and diffuse type 1-3 adenomyosis in anterior wall Extent: Severe Maximal diameter: 1. Focal lesion : 4cm 2. Diffuse lesion : 7cm
Yes	Anterior wall	Diffuse	Yes	Type 1-3	Severe >50%	7cm	

FIGURE 2. MUSA criteria for adenomyosis



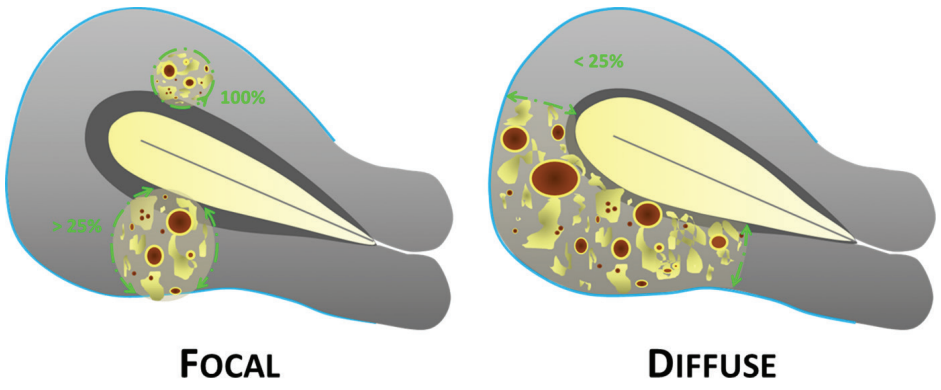
Note: Adapted from Van den Bosch, Dueholm et al[1]

2) The location of the adenomyosis is described. It should be described as anterior, posterior, lateral left, lateral right or fundal. To determine the exact location, the uterus should be examined in both sagittal and transverse planes. The additional value of three-dimensional (3D) ultrasound to examine the coronal plane of the uterus needs to be established in future studies.

3) Discriminate between focal and diffuse adenomyosis in each location. To define an adenomyotic lesion as focal we propose the following criteria must be fulfilled: more than 25% of the circumference of the lesion must be surrounded by normal myometrium provided that less than 25% of the myometrium of the corpus uteri is involved. These percentages are estimated on sagittal section through the uterus where the adenomyotic lesion appears to be at its largest. In case of multiple focal lesions, the adenomyosis is classified as diffuse if the total involvement of the myometrium exceeds 25% of the corpus uteri. If it is difficult to differentiate a focal from a diffuse lesion, the lesion should be reported as diffuse adenomyosis. If there is both diffuse and focal adenomyosis in different locations

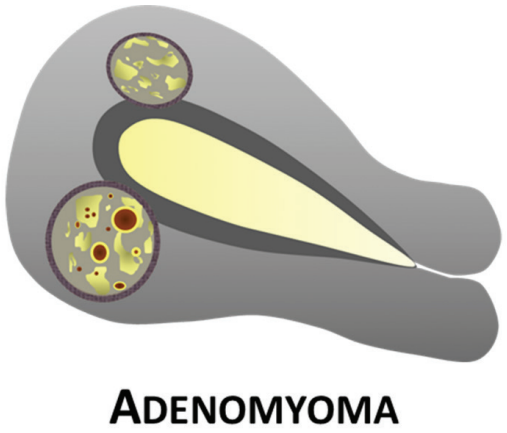
in the uterus this should be called "mixed type adenomyosis". Figure 3 illustrates the difference between focal and diffuse adenomyosis. Futures studies are needed to determine the value of using the transversal and/or coronal planes for discriminating between focal and diffuse adenomyosis. When focal adenomyosis is distinctly demarcated and surrounded by hypertrophic myometrium, it is called an adenomyoma [8]. Figure 4 shows the distinctly demarcated lesion.

FIGURE 3. Focal and diffuse adenomyosis



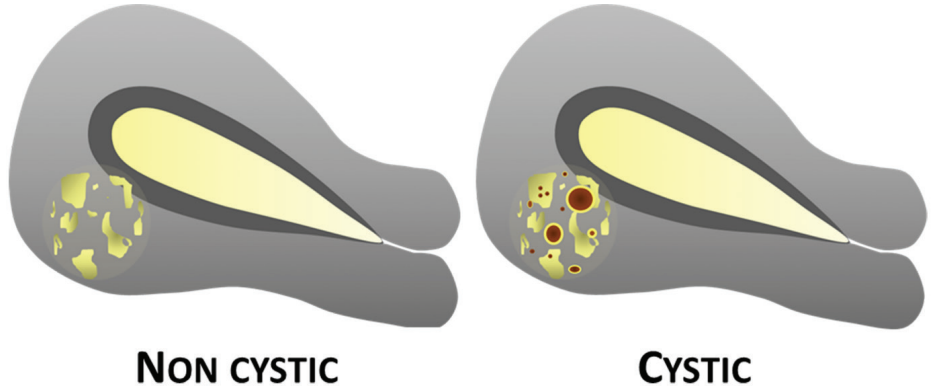
Note: Endometrium=yellow; Junctional zone (inner myometrium)=dark grey; myometrium (middle myometrium and outer myometrium)= grey; serosa is blue; focal if >25% of the lesion is surrounded by normal myometrium (i.e. the sum of the green dotted lines must represent more than 25% of the circumference of the lesion)

FIGURE 4. Adenomyoma



4) The adenomyosis is classified as cystic or non-cystic (Figure 5). Cysts should be reported in all types of adenomyosis (focal-, diffuse-, mixed-adenomyosis, adenomyoma). Adenomyosis is defined as cystic in the presence of measurable cysts. A myometrial cyst is considered measurable if the largest diameter is at least 2 mm. The cyst fluid is usually anechoic or of low level echogenicity, and the cysts may be surrounded by an echogenic rim. In a research protocol, it may be appropriate to measure the largest diameter of the largest cyst and to record the presence or absence of an echogenic rim.

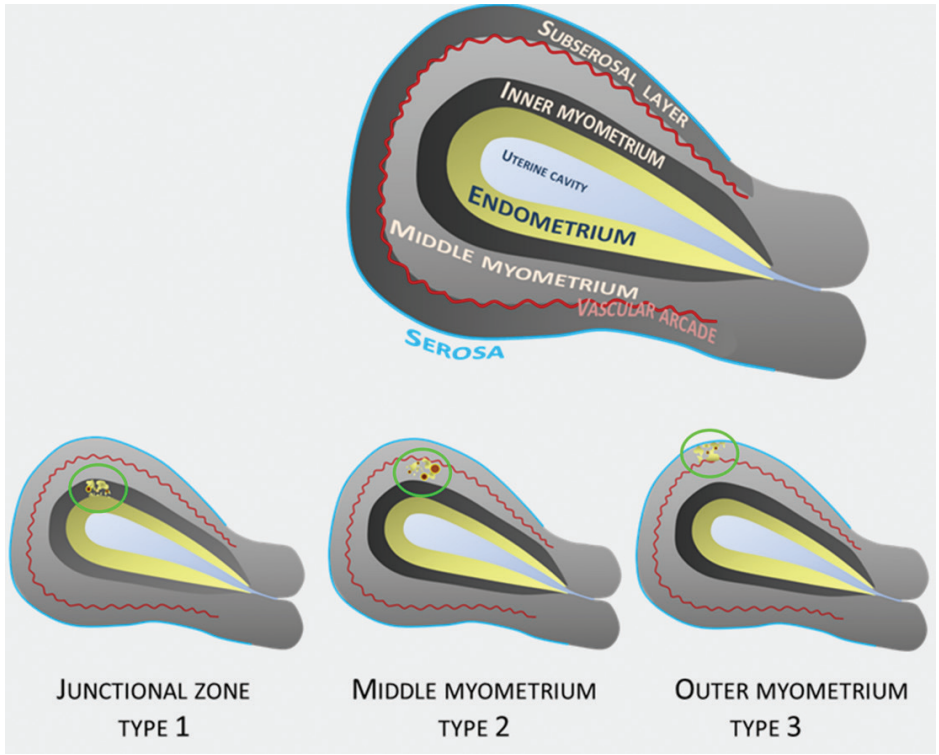
FIGURE 5. Focal adenomyosis divided into cystic and non-cystic



5) Evaluation of the involvement of the uterine layers. We found it relevant to specify involvement not only of the junctional zone but also of the other layers of the myometrium and the serosa. We speculated that the number and type of layers involved might be associated with the clinical presentation and depend on the etiology of adenomyosis. Adenomyosis may involve one or more of the following three layers: 1) the junctional zone (the inner myometrium also called the subendometrial layer consisting of longitudinal and circular closely packed smooth muscle fibres), 2) the middle myometrium (the myometrium between the vascular arcade and the junctional zone consisting of crisscrossing muscle fibres), 3) outer myometrium (the subserosal layer i.e the layer between the serosa and the vascular arcade) [17, 28, 32-34] (Figure 6). If the outer myometrium is involved the serosal layer may be intact or interrupted. To help identify serosal involvement of adenomyosis the presence of sliding of or fixed viscera [32] (bowels) against the

uterus should alwaysbe recorded. In this work we do not comment on ultrasound examination with regard to concomitant superficial or deep endometriosis [35]. The involvement of one of the 3 layers is recorded as type 1, type 2 or type 3 (Table 1). If more than one layer is involved, the type is recorded and described as follows: type 1-2 or type 2-3. To differentiate between involvement of the subserosal layer and middle myometrium layer it may help to use color Doppler and estimate the location in relation to the vascular arcade. Future studies are needed to determine if it is feasible to differentiate between three muscle layers, and if there is any clinical value of differentiating between the middle and outer myometrium.

FIGURE 6. Layer infiltration of adenomyosis



Note: Endometrium=yellow; Junctional zone (inner myometrium)=dark grey; Middle myometrium=grey, located between the vascular arcade and junctional zone; Outer myometrium (subserosa)= grey and located between the vascular arcade and serosa; Serosa interruption=blue

6) The extent of the disease should be subjectively assessed (mild, moderate or severe adenomyosis). The extent is based on the estimated volume of the

uterine corpus affected by adenomyosis: 1) mild <25% 2) moderate 25-50% or 3) severe >50%. If there are adenomyotic lesions in different locations, the sum of volumes of the different lesions should be estimated when describing the extent of the disease. The subjectively estimated extent of the disease might not be associated with the type or severity of symptoms but may be useful for research purposes.

7) The size of the adenomyosis lesion(s) should be measured. In a research protocol the largest diameter of each focal lesion might need to be recorded. It should be measured in the plane with the largest diameter r. In case of a diffuse lesion the myometrial wall thickness needs to be measured and the site involved noted. Future studies are needed to estimate the additional value of assessing the size in three orthogonal planes.

FINAL CONCEPT

We propose a consensus based practical classification of adenomyosis on the basis of ultrasound findings (Figure 7): 1) stating the presence of a myometrial abnormality based on the MUSA criteria; 2) location of adenomyosis; 3) differentiation between focal and diffuse disease; 4) discrimination between cystic and non-cystic lesions; 5) myometrial layer involvement; 6) classifying disease extent as mild, moderate or severe; 7) size of the lesion. Cycle day and current hormonal use should always be recorded.

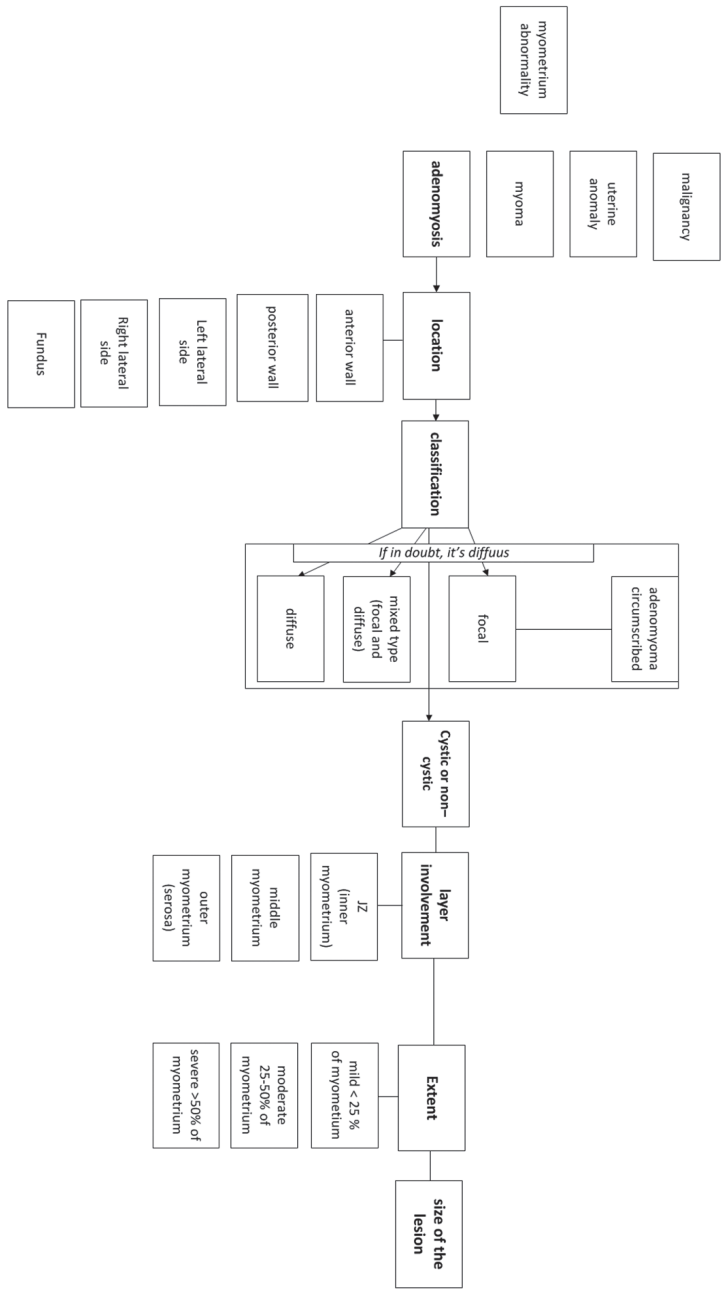


FIGURE 7. Classification and reporting guideline for ultrasonographic features of adenomyosis

Note: JZ = Junctional zone

CONCLUSION AND DISCUSSION

This classification should facilitate consistent reporting but it needs to be validated and refined after future studies. For example the feasibility and reproducibility of the differentiation between the middle and outer myometrial layer using power Doppler needs to be assessed. Also the additional value of the use of the transversal and/or coronal planes (the latter using 3D-ultrasound) for the assessment of the localization, extent and size of adenomyotic lesions needs to be investigated in future studies. Although the consensus has been developed using the MUSA terms and definitions, we propose some changes. When using the original MUSA terminology an 'ill-defined lesion' may be localized or diffuse, the latter being a lesion involving at least 50% of the total uterine volume1. We suggest reporting the adenomyosis as focal or diffuse in each location. For example, it should be possible to report focal adenomyosis in the anterior wall and diffuse adenomyosis in the posterior wall, using the definition of focal disease outlined above. A second slight adjustment is the specification of the myometrial layer involved. Research is needed to assess the accuracy of ultrasound examination in the diagnosis of focal versus diffuse adenomyosis. In a prospective case series assessing uterine lesions in hysterectomy specimens, some adenomyosis lesions appeared to be much more extensive than suspected at ultrasonography or on macroscopic examination [36]. The possibility of diffuse disease not detected at ultrasound examination should be borne in mind when planning management of patients with adenomyosis and when planning studies. Recent studies showed that the number of morphological features of adenomyosis was associated with clinical symptoms and success of fertility treatment [37-39]. However, more research is needed to evaluate to importance of each of the different ultrasound features. It is the clinical experience of the authors that some women with small lesions may present with severe symptoms of pain and uterine bleeding, whereas others with larger lesions may be asymptomatic. Clearly, the classification we have suggested cannot be used on its own to decide on treatment. The proposed classification might need to be amended after external validation and based on the results of future studies evaluating the relation between ultrasound features, clinical symptoms, histological findings and possibly also MRI-findings. There are still uncertainties regarding the clinical importance of myometrial cysts, the relevance of discriminating between the uterine layers and the reliability of estimating disease extent. A study addressing the intra- and interobserver variability using the proposed reporting is also needed. Our suggested approach should be considered only as a first step towards an internationally accepted classification and reporting system. We recognize that some aspects

of the suggested reporting and classification system might require extensive ultrasound skills. After validation and optimization of the proposed classification, it would be reasonable to develop an e learning program for less experienced ultrasonographers.

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SUPPLEMENTARY MATERIAL

APPENDIX 1. CONSENSUS RESULTS

			Consensus meeting	Delphi procedure		
Item	**Questions**	**No. of questions**		**Round 1 (%)**	**Round 2 (%)**	**Round 3 (%)**
1: Myometrium classification	Classification and assessment of a uterus with adenomyosis	8	100	c	c	c
	Description of location	1	100	c	c	c
	Location in sagittal and transverse planes	1	100	c	c	c
	Role of three-dimensional ultrasound	1	100	63*	63	75
3. Differentiation diffuse/focal	Adenomyosis on ultrasound in the sagittal plane(Diffuse/ Focal/mixed)	3	100	63*	63	100
	Adenomyoma	1	63	75	c	c
4: Cystic or non-cystic	Cyst size >2mm	3	NA	50	88-100	c
	Defining cysts by size	2	NA	88	c	c
	Reporting cysts in diffuse, focal and mixed adenomyosis	2	NA	88	c	c
5: involvement of uterine layers	Three myometrial layers	2	63	75-88	c	c
	Reporting sliding viscera	6	NA	63-75	88-100	c
6: Extent of adenomyosis	Extent: mild, moderate and severe	1	100	c	c	c
7: Size of the lesion	Size of lesion	1	100	c	c	c
	Measure the maximum diameter in the plane where the lesion appears to be at its largest.	2	63	75-88	c	c
Additional information	Always register cycle day and hormonal therapy, but not in flow diagram.	4	63	88	100	c

Note: This table presents the mean consensus per item. When consensus was reached (green marking), the item was excluded from the next Delphi round. In the table this is presented as 'c' (consensus achieved). * additional questions were raised by the steering committee during the reviewing process resulting in a lower consensus rate than 100%. The number of questions column displays the total number of questions related to the subject during the consensus meeting and all rounds of the Delphi procedure.

PART III

SUMMARY, GENERAL DISCUSSION AND CONCLUSION

9

Summary, general discussion, future research and conclusion

SUMMARY

This thesis aimed to position uterine artery embolization (UAE) as treatment option for uterine fibroids and adenomyosis. This was presented in two parts of this thesis:

PART I

This part of this thesis evaluated UAE for uterine fibroids, which has been applied for over 20 years, one step further by looking at long term outcomes, implementation in the Netherlands and its applications in an unusual indication (cervical fibroids). In order to be able to counsel patients on long term outcomes, counseling information for gynecologist and stimulate implementation into daily practice, the 10 year follow-up of EMMY trial patients was conducted. In addition an UAE implementation inventory and preference study was set up to assess implementation of UAE and investigate the hampering of factors for the application of UAE. Since we noticed that UAE efficacy and safety in patients with symptomatic cervical located fibroids were not yet evaluated, a case series was published to initiate further research and possibly expand the therapeutic applicability of UAE.

PART II

This part of the thesis makes the first steps towards positioning uterine artery embolization in the spectrum of treatments for symptomatic adenomyosis, as a relatively new treatment modality for this disease. To do this, the following aspects of UAE were investigated; 1) a seven-year clinical follow-up of patients with symptomatic adenomyosis treated with UAE was conducted and published, 2) a systematic review and meta-analysis of the current available literature was performed. This review evaluated short term and long term treatment effect of UAE in patients with symptomatic adenomyosis. The outcomes seemed promising, however no comparative trials (level 1 evidence) is available. As a result too strong conclusions could not be drawn, therefore we set up step 3) the QUESTA (*Quality of Life after Embolization vs Hysterectomy in Adenomyosis*). This is a randomized controlled trial comparing uterine artery embolization and hysterectomy in the treatment of patients with symptomatic adenomyosis. This thesis describes the design of this trial. The outcomes are not part of this thesis (the trial is still recruiting).

During the inclusion period of the QUESTA trial we noticed difficulties in diagnosing adenomyosis. It seems adenomyosis is a frequently unrecognized benign disease or mistaken for uterine fibroid disease. Gynecologists indicated lack of knowledge concerning the disease, imaging characteristics and

possible treatment options. Since treatment management is often based on an ultrasonographic based diagnosis of adenomyosis only, a uniform reproducible and clinically relevant reporting system was developed.

The above mentioned performed studies as described in this thesis will be summarized in the next paragraphs, together will a general discussion that compares our results with current literature. Thereafter the implication of this thesis will be mentioned together with an overall conclusion and indications for future research.

RESULTS

MAIN FINDINGS PART I: UTERINE FIBROIDS

LONG TERM RESULTS OF UAE: THE RANDOMIZED EMMY TRIAL

In chapter 2 we described the 10-year follow-up results of the EMMY (Embolization versus hysterectomy) trial, a randomized comparison between UAE and hysterectomy. Patients with symptomatic uterine fibroids were randomly (1:1) allocated to UAE or hysterectomy and previously followed up until 5 years after treatment. Endpoints after 10 years were re-interventions, quality of life, urinary and defecation function, menopausal symptoms, menstrual characteristics and satisfaction with the received treatment. 177 patients were randomized between 2002 and 2004. Eventually 81 uterine artery embolization and 75 hysterectomy patients underwent the allocated treatment shortly after randomization. Between 5 and 10 years after treatment 5 patients additional underwent secondary hysterectomy resulting in a total of 28/81 re-interventions (35%). In case of successful uterine artery embolization, excluding UAE procedure failure. it resulted in a total of 24/77 (31%) hysterectomies. Secondary hysterectomies were performed for persisting/recurrent complaints in all cases but one (1 for prolapse). After the initial treatment health related quality of life improved significantly and remained stable, without differences between both groups. The urogenital distress inventory and the defecation distress inventory showed a decrease in both groups, probably related to increasing age, without significant differences between study arms. The majority of patients declared to be (very) satisfied about the received treatment and this remained comparable in both groups. We concluded that in about two-thirds of uterine artery embolization treated patients with symptomatic uterine fibroids a hysterectomy can be avoided. Based on these outcomes, Uterine artery embolization is a well-documented less invasive alternative to hysterectomy for symptomatic uterine fibroids on which eligible patients should be counseled.

IMPLEMENTATION OF UAE: AN INVENTORY AND PREFENRENCE STUDY

Chapter 3 describes an inventory and preference study that aimed to find out if the 2013 national guideline had any effect on UAE implementation and to assess the different aspects of UAE counseling, preference, difficulties and knowledge/awareness among gynecologists. In order to observe the quantity of performed UAE in the Netherlands, the 2012, 2013 and 2014 annual reports of all hospitals were requested and used to establish the overall UAE/hysterectomy ratio. Secondly, questionnaires were filled in by gynecologists working at UAE performing (UAE+) and non-UAE performing (UAE-) hospitals resulting in a group comparison analysis. The UAE/hysterectomy ratio before (2012) and after (2014) incorporation in the 2013 guideline remained low and were 7.0 % and 6.9 %, respectively. Outcomes of the questionnaires filled in by gynecologists showed that the availability of UAE influences the frequency and type of counseling in patients with symptomatic uterine fibroids. UAE+ hospitals estimate higher counseling numbers compared to UAE- hospitals. Approximately 50% of gynecologists working in UAE- hospitals indicated that they have insufficient information about UAE for appropriate counseling and in the majority of gynecologists from both hospitals they overestimate the risk of re-intervention. We concluded that it might be useful to develop an option grid or decision making tool in order to offer independent counseling and encourage shared decision making.

UAE IN THE TREATMENT OF CERVICAL FIBROIDS.

In chapter 4 we performed an evaluation on safety and efficacy of uterine artery embolization (UAE) in the patients with symptomatic cervical fibroids. The 3 month outcomes were assessed with MR imaging and a validated questionnaire. Between 2006 and 2017, 8 patients underwent UAE and were retrospectively analyzed. At 3 months, all patients showed cervical leiomyoma volume reduction with a median reduction of 41.5% (38.8 cm3) compared to baseline (p=0.012). No complications occurred. At a median follow-up of 3 months (range 1-7, n=7) the validated HRQOL and SSS scores improved with a median difference of 13 points (range -5-60, p=0.063) and -13 points (range -79-3, p=0.046), respectively. Long term follow-up showed two secondary interventions (median of 43.5 months). Six patients reported no symptom recurrence. We concluded that UAE in women with symptomatic cervical fibroids is effective and safe with significant improvement of symptoms and quality of life. It seems a valuable option for women seeking a non-surgical solution or when operative intervention is too dangerous.

MAIN FINDINGS PART II: ADENOMYOSIS

7 YEAR FOLLOW-UP OF UAE IN PATIENTS WITH ADENOMYOSIS

In chapter 5 we assessed clinical outcomes seven years after uterine artery embolization in the treatment of symptoms caused by symptomatic adenomyosis. The seven year post-intervention outcomes were health related quality of life (HRQOL), symptom severity scores (SSS), patient satisfaction, menopause and re-intervention rates which were assessed with standardized questionnaires. Twenty-nine patients with adenomyosis (15 in combination with fibroids) were included and treated with UAE between September 2006 and January 2010. Previously results were published 3 years after treatment. Seven years after treatment 5 of 28 patients (18 %) had a secondary hysterectomy due to persisting complaints. The initially significantly improved HRQOL after UAE remained stable throughout the years up unto seven years. The SSS showed a small statistical significant difference in favor of the adenomyosis in combination with fibroids group compared to the pure adenomyosis group. We concluded that in 82% of patients UAE results in preservation of the uterus. 72% of patients are satisfied and two third seem to respond well to UAE in terms of improvement of HRQOL and SSS.

A SYSTEMATIC REVIEW AND METANALYSIS ON UAE IN THE TREATMENT OF ADENOMYSOSIS

Chapter 6 described the result of a systematic review and meta-analysis that evaluated the effect of uterine artery embolization (UAE) on symptomatic adenomyosis. We evaluated patients from 30 prospective and retrospective cohorts. Four groups were evaluated: short-term (< 12 months) pure adenomyosis, short-term adenomyosis with fibroids (combined adenomyosis), long-term (> 12 months) pure adenomyosis, and long-term combined adenomyosis. Improvement of symptoms occurred in 83.1% (872/1049) of patients. Reported symptom reduction was 4.8% greater in the short-term combined group (P = 0.169) and 11.4% greater in the long-term combined group (P = 0.003) compared to pure adenomyosis groups. Hysterectomy rate in the short term group varied from 2.6% in the pure adenomyosis group and 1.4% in the combined group. The long term group showed a comparable hysterectomy rate of 7.2% in the pure adenomyosis group compared to 7.0% in the combined group. The weighted absolute uterine volume reduction at 3 months was reduced in all patients, however it was statistically greater in the pure adenomyosis group. We concluded that the effects of UAE on symptom improvement and uterine volume reduction in patients with adenomyosis seem encouraging, however more evidence is required before routine use in clinical practice can be justified.

QUESTA TRIAL STUDY PROTOCOL

In chapter 7 we described the study protocol of the QUESTA trial, a multicenter randomized trial comparing UAE and hysterectomy. We designed this trial to provide insight in the effectiveness of UAE versus hysterectomy in terms of quality of life after 6, 12 and 24 months following assigned intervention. Secondary objectives were technical results, imaging outcomes for trans vaginal ultrasonography/magnetic resonance imaging, pain management, clinical outcomes, recovery related outcomes, laboratory outcomes, Pathology outcomes, HRQOL, and cost effectiveness during 24 months of follow-up. We aimed to include 96 patients in this trial.

SONOGRAPHIC CLASSIFICATION AND REPORTING FOR ADENOMYOSIS.

Chapter 8 presents a uniform classification and standardized reporting system of ultrasound findings of adenomyosis using the Morphological Uterus Sonographic Assessment (MUSA) criteria. This classification and reporting system was built based on a thorough discussion among all authors, including a Delphi procedure. Selected images and videos of typical cases of the different morphological variations of adenomyosis were used in the debates.

This system includes: (1) identification of adenomyosis based on MUSA criteria, (2) disease location, (3) classification of the lesions as focal or diffuse, (4) presence or absence of intralesional cysts, (5) myometrial layer involvement (junctional zone, myometrium, serosal involvement), (6) disease extent and (7) lesion size. The proposed classification might need to be amended after external validation and based on the result of future studies evaluating the relation between ultrasound features, clinical symptoms, histological finding and possibly also MRI findings.

GENERAL DISCUSSION

UAE IN THE TREATMENT OF FIBROIDS.

Uterine artery embolization (UAE) is one of the minimally invasive treatments options for uterine fibroids. This treatment was introduced in 1995 by Ravina et al [1]. Since then multiple randomized controlled trials and a Cochrane review have been published and concluded that UAE is a safe alternative for surgery in terms of quality of life and treatment satisfaction rates [2]. One of these trials is the Dutch randomized EMMY trial (embolization versus hysterectomy). During the 10 year follow-up we noticed that the most striking increase in HRQOL in both study arms occurred in the first 6 months after treatment and remained stable for 10 years without differences between both groups [3]. Most secondary hysterectomies

(23.5%) occurred in the first 2 years of follow-up. The 5 years follow-up of the EMMY trial reported an additional four hysterectomies due to insufficient improvement of bleeding complains, resulting in a secondary hysterectomy rate of 28.4% [4, 5], these findings were comparable to the secondary hysterectomy rate in the 5-year follow-up of the randomized REST trial (Randomized controlled trial of Embolization versus Surgical Treatment) [6]. The EMMY trial is the only study on UAE for fibroids ever published with 10 years of follow-up, therefore it provides clinicians with unique insight for patient counseling in term of clinical outcomes and various aspects of quality of life. It concluded that after 10 years of follow-up, in 69% of all women undergoing a technical successful UAE, a hysterectomy was avoided and quality of life remained comparably stable between study arms [3]. Despite the evidence from the multiple randomized controlled trials UAE was not being offered in a daily practice. In 2011, a pilot study [7] showed that UAE was not being offered as an alternative to surgery because of the absence of UAE as a treatment option in the Dutch guideline on heavy menstrual bleeding (HMB). Therefore the EMMY trial study group initiated the update of the national guideline for HMB in 2013. Experts in the field of HMB were asked to participate in the evidence based update of the guideline. All treatments for HMB were carefully reviewed resulting in a new evidence based guideline that had incorporated UAE for the first time in this guideline. Considering the outcome of the pilot study, we postulated that this would result in an improved implementation of UAE in the Netherlands [8]. The implementation and preference study as described in this thesis, found that the publication of the 2013 national guideline did not increase the number of performed UAEs. The main obstacle for implementation seems to be the persistence of 'urban embolization myths'; 40% of gynecologists in non-UAE performing hospitals doubt effectiveness of UAE and nearly half of gynecologists in UAE performing hospitals overestimate the chance of a surgical intervention after UAE [9]. In view of the short- and long-term available clinical and quality-of-life evidence, we concluded –again- that all women who are candidates for hysterectomy because of symptomatic uterine fibroids should be counseled on the option of UAE. Also, the counseling content deserves attention: only mentioning UAE is not enough, patients should have an adequate independent counseling irrespective of the treating gynecologist. When UAE is not available in that specific hospital a clear-cut route of referral needs to be available.

While conducting the EMMY trial 10 year follow-up, we studied the applicability of UAE as a minimally invasive option in patients that might be more of a surgical challenge, therefore a retrospective study of UAE in the treatment of patients with

symptomatic cervical fibroids was conducted [10]. We concluded that UAE in these patients seems effective and safe with significant improvement in symptoms and quality of life, however it was a very small sample size (n=8). Compared to the only other small retrospective study [11] we reported a higher success rate, however they did not use validated questionnaires. The difference in outcome might be explained by vascularity variety, smaller fibroids and thus less infarction in their population or a different catheterization technique. Since only these two reports are available implementation of UAE in the treatment of cervical fibroids is too preliminary. Larger high quality trials should ideally be conducted to confirm our results. However, this condition is rare, so large prospective studies in the future seem unlikely. Since surgery can be risky with cervical fibroids, we hope our report contributed to taking UAE as a treatment option for these fibroids into account.

UAE IN THE TREATMENT OF ADENOMYOSIS.

Publications on the results after UAE in the treatment of adenomyosis increased in the last years, but evidence is still limited. Only 15 small uncontrolled case series were available when we started the evaluation of the 7-year follow-up of UAE in the treatment of patients with symptomatic adenomyosis. These 15 case series showed substantial improvement of symptoms (heavy menstrual bleeding, dysmenorrhea and bulk related symptoms) after UAE [12]. According to these uncontrolled series, clinical effectiveness, defined as improvement of heavy menstrual bleeding, dysmenorrhea and bulk related symptoms, averaged 75.7%. The longest follow-up among one of these case series was 60 months. It justified the evaluation of longer follow-up and as far as we are aware of, our prospective cohort is the longest follow-up available so far. The most noticeable improvement of HRQOL in patients with pure adenomyosis and in adenomyosis with fibroids occurred in the first 3 months after UAE and remained stable over time without differences between the two groups. At follow-up, the symptoms severity score showed comparable stable improvement with a small statistical difference in favor of the adenomyosis combined with fibroids group at 3, 37 and 92 months. This finding is concordant with our systematic review and meta-analysis [13], but could also be explained by the initial selection bias where patients with pure adenomyosis had worse symptoms compared to the patients with adenomyosis and fibroids. A total of five patients underwent a secondary hysterectomy (18%). Four of these five patients had hysterectomy after the earlier reported 37-month follow-up interval [14]. When comparing our results to other long term prospective cohorts we noticed that Bae at al reported only one secondary hysterectomy

at 18 months in a total follow-up of 48 months [15]. This rate was not comparable to our study and could possibly be explained by; (1) the selected group of patients in our study with possibly worse baseline symptoms and no other option than a hysterectomy and 2) a longer follow-up than any other study in which we demonstrate that even at 55 and 80 months secondary hysterectomies are performed. Another long term follow-up study using validated questionnaires showed comparable outcomes at a follow-up of 46 months [16].

The continued increase in patients undergoing hysterectomy underlines the importance of long-term follow-up. It could provide insights for prediction of quality of life, recurrence of symptoms, costs and possibly counseling of patients. During evaluation of the prospective cohort for long term treatment effects of UAE in patients with adenomyosis, we systematically searched the literature for more up to date publications and conducted a systematic review and meta-analysis [13]. In this review we concluded that UAE has favorable short-term and long-term outcomes whether it is performed for pure adenomyosis or adenomyosis in combination with fibroids. The included studies reported improvement of clinical symptoms, defined as improvement of heavy menstrual bleeding, dysmenorrhea and bulk related symptoms, in 83.1% (872 of 1049) of patients. Greater JZ thickness (> 23 mm) and low infarction rates (< 34.4%) have been associated with decreased effectiveness for UAE in treating adenomyosis. What hampered this review was the heterogeneity of studies, no available (randomized) controlled trials, small sample size and under-reporting of excluded patient or patients lost to follow-up, therefore selection bias and publication bias could not be ruled out. In addition no validated adenomyosis-specific questionnaires available. As a result of these limitations this review does not support too strong clinical conclusions regarding UAE in the treatment of symptomatic adenomyosis. It needed to be confirmed in comparative (preferably randomized) trials before implementation in daily practice.

Resulting in the development of the QUESTA (Q*uality of Life after* E*mbolization vs Hysterectomy in* A*denomyosis*) to evaluate the true effectiveness of UAE in comparison to hysterectomy, however during the inclusion period patient inclusion was difficult. It mostly seemed hampered by poor recognition of adenomyosis on ultrasound. Therefore a uniform reproducible and clinically relevant reporting system was developed.

SONOGRAPHIC IMAGING IN DIAGNOSING ADENOMYOSIS

Many reports publish that transvaginal ultrasonography is now considered the primary imaging modality for diagnosing adenomyosis [17, 18]. Before publication

of a recent consensus statement describing terms, definitions and measurements that may be used in the ultrasonographic description of adenomyosis, the extent of criteria and methods used for diagnosing adenomyosis on ultrasonography used to vary between studies [19]. This consensus statement is a positive step toward a unified nomenclature for research and classification in adenomyosis. Naftalin et al showed a good level of agreement between histology and ultrasonographic diagnosis of adenomyosis by the use of the MUSA criteria, however all ultrasonographic diagnosis of adenomyosis were determined by one single operator [18]. Since the MUSA criteria have never been validated, it was reasonable to asses the use of the MUSA criteria by the mean of an intra-inter observer study in order and establish the use of these criteria as a reliable method for clinical practice.

Since the MUSA consensus statement does not provide guidelines for how to classify morphological types or extent of adenomyosis. The classification and reporting system as described in this thesis was conducted. It should facilitate consistent reporting and a guideline for classifying the above mentioned ultrasonographic features [20]. However it needs to be validated and refined after future studies. Some issues have risen during the development of the classification and reporting system including; 1) research is needed to assess the accuracy of ultrasound examination in the diagnosis of focal versus diffuse adenomyosis. In a prospective case series assessing uterine lesions in hysterectomy specimens, some adenomyosis lesions appeared to be much more extensive than suspected at ultrasonography or on macroscopic examination [21]. The possibility of diffuse disease not detected at ultrasound examination should be born in mind when planning management of patients with adenomyosis and when planning studies. 2) evaluation if morphological features of adenomyosis is associated with clinical symptoms and success of fertility treatment. Some recent studies seem to show an association [18, 22, 23], however more research is needed to evaluate the importance of each of the different ultrasound features. The classification we have suggested cannot be used on its own to decide on treatment, but needs to be validated first.

FUTURE RESEARCH

The embolization implementation process (the use and compliance of the heavy menstrual bleeding guideline) was tested by the use of embolization/ hysterectomy ratio's in women with symptomatic fibroids. It shows that it might be useful to develop an option grid or decision-making tool in order to offer independent counseling, encourage shared decision making and increase

implementation of UAE. This evaluation was part in the so-called 'circle of quality'('kwaliteitscirkel in Dutch) as designed by the EMMY trial group. Furthermore, the guideline should be updated with the new evidence of UAE versus hysterectomy after 10-years.

In this thesis we describe the still ongoing randomized controlled QUESTA trial (*Quality of Life after Embolization vs Hysterectomy in Adenomyosis*). This trial might establish the role of UAE in women suffering from symptomatic adenomyosis. Besides this, the role of UAE as well as other minimally invasive alternatives (e.g MRgFUS, myomectomy) in the treatment of women that have a wish to conceive in the future deserves to be investigated.

Besides investigating future treatment options for adenomyosis, we recommend the use of the standardized UFSQOL questionnaire in all future studies to have congruous and comparable outcomes [24]. Futhermore diagnosing adenomyosis is still challenging. We proposed a uniform ultrasonographic classification and reporting system in diagnosing adenomyosis. After validation and optimization of the proposed classification by means of a inter and intra-observer validation study, it would be reasonable to develop an e-learning program for less experienced ultrasonographers.

Furthermore, the classification also needs to be amended after external validation based on the results of future studies evaluating the relation between ultrasound features, clinical symptoms, histological findings and possibly also MRI-findings.

CONCLUSION

In conclusion, this thesis investigated the long term randomized controlled evidence on UAE for fibroids, evaluated the implementation of UAE after incorporation of UAE in the Dutch guideline on heavy menstrual bleeding and investigated the use of UAE in the treatment of cervical fibroids in a small case series. We demonstrated that UAE offers a long term valuable alternative to hysterectomy and is non-inferior in terms of HRQOL. Implementation of UAE after incorporation in the Dutch guideline did not increase embolization/hysterectomy ratio's. This might be due to the perseverance of 'urban myths' about the effectiveness and side-effects. We hope that in the future an option grid or decision-making tool might support implementation. We consider it substandard care if UAE is not being offered as part of a treatment option in patients with symptomatic fibroids. Standardized independent information is important in order to let the patient make a good choice

UAE in the treatment of adenomyosis seems promising, however it still has to be confirmed in well set up and good quality trials before implementation in daily practice.
Ultrasonographic diagnosis of adenomyosis seems challenging due to lack of training and recognition of the relatively new published criteria for adenomyosis. The uniform reporting and classification system as described in this thesis should support consistent reporting.

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10

Samenvatting en conclusie

SAMENVATTING

Dit proefschrift is gericht op het positioneren van uterus embolisatie als behandeloptie van myomen en adenomyose in de Nederlandse praktijk. De onderzoeken en resultaten hiervan worden gepresenteerd in twee delen van dit proefschrift:

DEEL I

Dit deel van het proefschrift evalueert embolisatie als behandeloptie van myomen door te kijken naar lange termijn resultaten, implementatie van uterus embolisatie in Nederland en de toepasbaarheid in de behandeling van cervicale myomen. De 10 jaar durende follow-up van het EMMY-onderzoek werd uitgevoerd om 1) patiënten en gynaecologen goed te kunnen informeren en adviseren over de uitkomsten van embolisatie op lange termijn en 2) implementatie ervan in de dagelijkse praktijk te stimuleren. Daarnaast werd een inventarisatie en preferentieonderzoek uitgevoerd om de implementatie van embolisatie te beoordelen en belemmerende factoren hierin te onderzoeken. Onbekend was nog de mate van werkzaamheid en veiligheid van embolisatie in het geval van patiënten met symptomatische cervicale myomen. Dit resulteerde in een onderzoek en publicatie om zodoende de therapeutische toepasbaarheid van embolisatie te vergroten.

DEEL II

Dit deel van het proefschrift beschrijft embolisatie als een relatief nieuwe behandelmethode van adenomyose. De volgende onderzoeken werden opgezet en gepubliceerd; 1) een zeven jaar durende klinische follow-up van patiënten met symptomatische adenomyose behandeld met embolisatie en 2) een systematische review en meta-analyse van de huidige beschikbare literatuur over het korte- en lange termijn behandeleffect van embolisatie bij patiënten met symptomatische adenomyose. De uitkomsten leken veelbelovend. Er zijn echter geen vergelijkende onderzoeken (niveau 1-bewijs) beschikbaar. Als gevolg hiervan kan een betrouwbare conclusie niet worden getrokken. Deze uitkomst leidde tot de opzet van de gerandomiseerde QUESTA studie (kwaliteit van leven na embolisatie versus hysterectomie bij adenomyose). Deze studie vergelijkt embolisatie met hysterectomie als behandeling van patiënten met symptomatische adenomyose. Dit hoofdstuk beschrijft het protocol van deze studie waarvan momenteel de inclusies nog lopen. Derhalve zullen de resultaten van deze studie niet beschreven worden. Tijdens de inclusieperiode van de QUESTA-studie zagen we dat het diagnosticeren van adenomyose moeilijk bleek.

Het wordt vaak niet herkend of het wordt aangezien voor myomen. Gebrek aan kennis over het klinische ziektebeeld, de beeldvormingskenmerken en mogelijke behandelingsopties van adenomyose werden benoemd als oorzaken van deze onder diagnostiek. Gezien het feit dat de behandeling vaak alleen gebaseerd is op een echografische diagnose, werd er een uniform reproduceerbaar en klinisch relevant echografisch classificatiesysteem voor adenomyose ontwikkeld. De gedetailleerde resultaten van bovengenoemde onderzoeken zoals beschreven in dit proefschrift zullen in de volgende paragrafen worden samengevat.

RESULTATEN

Hoofdstuk 1 beschrijft de algemene introductie.

DEEL I. UTERUS EMBOLISATIE VAN MYOMEN
LANGE TERMIJN UITKOMSTEN VAN HET EMMY-ONDERZOEK.

Hoofdstuk 2 beschrijft de 10-jaars uitkomsten van het EMMY-onderzoek. Deze gerandomiseerde studie vergelijkt embolisatie met hysterectomie bij de behandeling van patiënten met symptomatische myomen. Patiënten met symptomatische myomen werden 1:1 gerandomiseerd voor embolisatie of hysterectomie. Deze patiënten werden voorheen 5 jaar gevolgd. De onderzoeksuitkomsten na 10 jaar waren re-interventies, kwaliteit van leven, mictie- en defecatiescores, menopauze, menstruatie karakteristieken en tevredenheid met de toegewezen behandeling. Tussen 2002 en 2004 werden 177 patiënten gerandomiseerd waarvan uiteindelijk 81 patiënten een embolisatie ondergingen en 75 patiënten een hysterectomie. Tussen de 5 en 10 jaar na de behandelingen werden er in de embolisatie groep nog 5 extra hysterectomieën uitgevoerd. Dit resulteerde in een totaal van 28/81 re-interventies (35%) in de gehele gelote embolisatie groep. In het geval van de embolisatie groep, met uitzondering van de initieel gefaalde embolisatie procedures, resulteerde dit in een totaal van 24/77 (31%) hysterectomieën. Secundaire hysterectomieën werden uitgevoerd in verband met aanhoudende of terugkerende klachten met uitzondering van één patiënt (prolaps). Na de initiële behandeling verbeterde de kwaliteit van leven significant in beide groepen Dit bleef stabiel in tijd zonder verschillen tussen de beide groepen. De mictie- en defecatiescores lieten in beide groepen op lange termijn een vergelijkbare verslechtering zien. Een mogelijke oorzaak hiervan kan de toegenomen leeftijd zijn. De meerderheid van de patiënten verklaarden tevreden te zijn over de behandeling. Dit bleef in beide groepen vergelijkbaar.

IMPLEMENTATIE VAN EMBOLISATIE: EEN INVENTARISATIE EN PREFERENTIE STUDIE.

Hoofdstuk 3 presenteert de resultaten van de implementatie van embolisatie als behandeling van patiënten met symptomatische myomen in Nederland. Dit werd ondersteund door aantallen hysterectomieën en embolisaties zoals gerapporteerd in de ziekenhuis jaarverslagen van 2012, 2013 en 2014. Tevens werden factoren die de implementatie van embolisatie konden beïnvloeden in kaart gebracht. Informatie werd verkregen door middel van vragenlijsten die verstuurd werden naar gynaecologen werkzaam in wel en niet-emboliserende ziekenhuizen. De vragenlijsten gingen inhoudelijk in op factoren als advisering, counseling, moeilijkheden, kennis en voorkeuren. De embolisatie/hysterectomie ratio voor (2012) en na (2014) publicatie van de nieuwe richtlijn in 2013 was respectievelijk 7,0% en 6,9%. Uitkomsten van de vragenlijsten lieten zien dat de beschikbaarheid van embolisatie in het ziekenhuis de counseling beïnvloedt. Dit gaat met name over de kwantiteit van de embolisatie counseling en de manier van counseling (preferentie van de arts).

Gynaecologen werkzaam in emboliserende ziekenhuizen schatten in dat ze meer counselen dan hun collegae in niet-emboliserende ziekenhuizen. Ongeveer 50% van de gynaecologen werkzaam in niet-emboliserende ziekenhuizen geven aan onvoldoende kennis te hebben over embolisatie om goed te kunnen counselen. De meerderheid van de gynaecologen in beide ziekenhuizen overschatten het risico van een re-interventie. Dit betreft 46% in het emboliserende ziekenhuis en 87% in het niet-emboliserende ziekenhuis.

Wij concluderen dat het ontwikkelen van een keuzehulp mogelijk nuttig is om patiënten betere en onafhankelijke counseling te bieden om zo tot een betere besluitvorming te komen.

EMBOLISATIE ALS BEHANDELING VAN CERVICALE MYOMEN

Hoofdstuk 4 beschrijft de werkzaamheid en veiligheid van embolisatie als behandeling van symptomatische cervicale myomen. De resultaten na 3 maanden werden in kaart gebracht met een MRI van de uterus en een gevalideerde vragenlijst. Tussen 2007 en 2017 ondergingen 8 patiënten een embolisatie. Deze patiënten zijn retrospectief geanalyseerd. Op de MRI, 3 maanden na de ingreep, zagen we bij elke patiënte een gemiddeld significante afname van het myoom volume van 41,5% (38,8 cm^3) in vergelijking met de situatie voor behandeling (p=0,012). Ten tijde van de gemiddelde follow-up van 3 maanden verbeterden de kwaliteit van leven (HRQOL) en klachtenscores (SSS) met respectievelijk 13 punten (p=0,063) en -13 punten (p=0,046). Lange

termijn follow-up (mediaan 43,5 maanden) rapporteerde twee re-interventies op basis van klachten en 6 patiënten rapporteerden geen recidief van hun klachten. Wij concluderen dat embolisatie voor patiënten met symptomatische cervicale myomen effectief en veilig is. Het resulteert in significante verbetering van kwaliteit van leven en klachten. Embolisatie lijkt een waardevolle optie voor vrouwen die een nieuw chirurgische behandeling zoeken of voor vrouwen waarbij een chirurgische interventie te riskant is.

DEEL II. UTERUS EMBOLISATIE VAN ADENOMYOSE EN ECHOGRAFIE VOOR DE DIAGNOSE EN CLASSIFICATIE VAN ADENOMYOSE

EMBOLISATIE ALS BEHANDELING VAN ADENOMYOSE: 7 JAAR FOLLOW-UP

Hoofdstuk 5 beschrijft een 7 jaar durende follow-up studie van patiënten met symptomatische adenomyose behandeld met embolisatie. De uitkomsten werden in kaart gebracht met gevalideerde vragenlijsten. Deze uitkomsten bestaan uit kwaliteit van leven (HRQOL), klachtenscores (SSS), patiënt tevredenheid, menopauze en re-interventie cijfers. Negenentwintig patiënten met adenomyose (waarvan 20 in combinatie met myomen) werden initieel geïncludeerd en ondergingen een embolisatie tussen september 2006 en januari 2010. Eerdere uitkomsten, 3 maanden en 3 jaar na de embolisatie, zijn eerder gepubliceerd. Zeven jaar na de embolisatie kregen 5/28 patiënten (18%) alsnog een hysterectomie in verband met aanhoudende of recidiverende klachten. De initieel significant verbeterde kwaliteit van leven bleef stabiel gedurende 7 jaar. De klachtenscore liet een kleine significante verbetering zien in de groep patiënten met adenomyose en myomen in vergelijking met patiënten met pure adenomyose. Wij concluderen dat 82% van de behandelde patiënten hun uterus heeft behouden. Van de patiënten is 72% tevreden en twee derde lijkt goed te reageren op embolisatie op het gebied van kwaliteit van leven en klachtenverbetering.

SYSTEMATISCHE REVIEW EN METAANALYSE OVER UTERUS EMBOLISATIE ALS BEHANDELING VAN ADENOMYOSE.

Hoofdstuk 6 presenteert de resultaten van een systematische review en meta-analyse en evalueert het behandeleffect van embolisatie bij patiënten met symptomatische adenomyose. Dertig prospectieve en retrospectieve cohorts werden geïncludeerd voor analyse. Patiënten werden ingedeeld in 4 groepen: korte termijn pure adenomyose (<12 maanden), korte termijn adenomyose gecombineerd met myomen, lange termijn pure adenomyose (≥12 maanden),

lange termijn adenomyose gecombineerd met myomen (≤12 maanden). Bij 83,1% (872/1049) van de patiënten resulteerde embolisatie in verbetering van symptomen. De gerapporteerde afname van symptomen was 4,8% hoger in de korte termijn gecombineerde groep (p=0,169) en 11,4% hoger in de lange termijn gecombineerde groep (p=0,003) vergeleken met de pure adenomyose groepen.
Hysterectomie cijfers in de korte termijn groep varieerden van 2,6% in de pure adenomyose groep and 1,4% in de gecombineerde groep. De lange termijn groep liet vergelijkbare hysterectomie cijfers zien. In de pure adenomyose groep 7,2% en in de gecombineerde groep 7.0%. De afname van het absoluut uterien volume 3 maanden na de ingreep was bij alle patiënten afgenomen. De volumeafname in de pure adneomyose groep was echter significant hoger. Wij concluderen dat het effect van embolisatie op de symptoomverbetering en de afname van uterien volume veelbelovend lijkt. Er is meer hoog kwalitatief onderzoek nodig voordat embolisatie als routine behandeling ingevoerd kan worden in de praktijk.

QUESTA STUDIE PROTOCOL

Hoofdstuk 7 beschrijft het protocol van de gerandomiseerde QUESTA-studie (Quality of Life after Embolization vs. Hysterectomy in Adenomyosis). Een studie waarbij embolisatie en hysterectomie worden vergeleken bij de behandeling van patiënten met symptomatische adenomyose. De studie is opgezet in meerdere ziekenhuizen en heeft als doel inzicht te geven in de mate van effectiviteit van embolisatie in vergelijking met hysterectomie. De primaire uitkomstmaten zijn kwaliteit van leven bij 6, 12 en 24 maanden na de toegewezen behandeling. Secundaire uitkomstmaten zijn technische resultaten, uitkomsten beeldvorming (MRI en echo), pijn management, klinische uitkomsten, herstel gerelateerde uitkomsten, bloeduitslagen, pathologie uitkomsten en kosteneffectiviteit op 24 maanden na de behandeling. Het doel is om 96 patiënten met adenomyose te includeren.

ECHOGRAFISCHE CLASSIFICATIE EN UNIFORME DOCUMENTATIE VAN ADENOMYOSE.

Hoofdstuk 8 presenteert een, op consensus van internationale experts gebaseerde, praktische classificatie van adenomyose op basis van echografische bevindingen. Het classificatie en documentatie systeem is gebaseerd op een grondige en volledige discussie tussen alle experts. Geselecteerde beelden en video's van morfologische variatie van adenomyose

werden gebruikt in de discussies. Het classificatie en uniforme documentatie systeem bestaat uit: (1) Identificatie van adenomyose gebaseerd op de Morphological Uterus Sonographic Assessment (MUSA) criteria, (2) locatie van adenomyose in de uterus, (3) classificatie van de laesie als focaal of diffuus, (4) aanwezigheid/afwezigheid van cysten, (5) betrokkenheid van verschillende lagen myometrium (junctional zone, myometrium, serosa), (6) uitgebreidheid van de ziekte, (7) grootte van de laesie. De voorgestelde classificatie zal mogelijk nog aangepast moeten worden na externe validatie en/of na het bekend worden van resultaten van toekomstige studies welke de relatie tussen echokenmerken van adenomyose, MRI, klinische symptomen en histologische bevindingen publiceren.

CONCLUSIE

Dit proefschrift beschrijft onderzoeken en rapporteert de resultaten betreffende de lange termijn uitkomsten van embolisatie als behandeling van myomen, de implementatie van embolisatie en de werkzaamheid en veiligheid van embolisatie als behandeling van symptomatische cervicale myomen. Onze uitkomsten tonen aan dat embolisatie een waardevol lange termijn alternatief biedt voor hysterectomie met een vergelijkbare kwaliteit van leven. Implementatie van embolisatie na benoeming in de landelijke richtlijn is niet verbeterd en had geen toename van embolisaties tot gevolg. Dit is mogelijk een gevolg van onterechte gedachten over de effectiviteit en bijwerkingen van embolisatie. Wij hopen dat er in de toekomst een keuzehulp kan worden ontwikkeld om de implementatie te ondersteunen. Op basis van onze resultaten zijn wij van mening dat, wanneer een patiënte geschikt is voor hysterectomie in verband met hevig menstrueel bloedverlies bij myomen, de mogelijkheid van een embolisatie met haar besproken dient te worden. Wij beschouwen het als suboptimale zorg wanneer dit niet aangeboden wordt. Ook in de behandeling van symptomatische adenomyose lijkt embolisatie als behandeling veelbelovend. Dit zal echter nog bevestigd moeten worden in goed opgezette studies van hoge kwaliteit voordat het als behandeling geïmplementeerd kan worden in de dagelijkse praktijk.

PART IV

APPENDICES

LIST OF PUBLICATIONS, DANKWOORD, CURRICULUM VITAE

LIST OF PUBLICATIONS

A.M. de Bruijn, W. M. Ankum, J. A. Reekers, E. Birnie, S. M. van der Kooij, N. A. Volkers and W. J. Hehenkamp. Uterine artery embolization vs hysterectomy in the treatment of symptomatic uterine fibroids: 10-year outcomes from the randomized EMMY trial. *Am J Obstet Gynecol* 2016; 215: 745 e741-745 e712.

A.M. de Bruijn, M. Smink, P. N. M. Lohle, J. A. F. Huirne, J. W. R. Twisk, C. Wong, L. Schoonmade and W. J. K. Hehenkamp. Uterine Artery Embolization for the Treatment of Adenomyosis: A Systematic Review and Meta-Analysis. *JVIR 2017; 28: 1629-1642 e1621.*

de Bruijn, A. M., et al. "Uterine Artery Embolization for Symptomatic Adenomyosis: 7-Year Clinical Follow-up Using UFS-Qol Questionnaire." CVIR 2017; 40: 1344-1350.

de Bruijn, A. M., et al. "Uterine Artery Embolization Versus Hysterectomy in the Treatment of Symptomatic Adenomyosis: Protocol for the Randomized QUESTA Trial." JMIR Res Protoc 2018; 7: e47.

Bruijn de, A.M. Hehenkamp WJK. Smeets AJ. Lopez A. Huirne JAF. Lohle PNM. Uterine artery embolization in women with symptomatic cervical leiomyoma: efficacy and safety. CVIR 2019; 42: 371-380.

T. Van den Bosch, A. M. de Bruijn, R. A. de Leeuw, M. Dueholm, C. Exacoustos, L. Valentin, T. Bourne, D. Timmerman and J. A. F. Huirne. A sonographic classification and reporting system for diagnosing adenomyosis. *Ultrasound Obstet Gynecol* 2019; 53: 576-582

A.M. de Bruijn, Huisman J, Hehenkamp JK, Lohle P.N.M, Reeker J.A, Timmermans A, Twijnstra A.R.H Implementation of uterine artery embolization for symptomatic fibroids in the Netherlands: an inventory and preference study. CVIR Endovascular 2019; (in press).

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Alle lieve en hardwerkende verloskundigen, verpleegkundigen, arts assistenten en medewerkers van de afdeling gynaecologie en obstetrie. Wat heb ik veel van jullie geleerd en altijd fijn met jullie samengewerkt. Jullie maken dit vak compleet.

VU ONDERZOEKERS

Lieve gynaika's ofwel de onderzoekers jaarclub. Anke, Anouk, Eva, Henrike, Inge, Jorine, Joukje, Marit, Marjolein, Mirte, Nicole, Sanne en Wieke. Wat een heerlijke tijd was het met jullie. Wie had ooit kunnen denken dat collega's zulke goede vrienden worden die elkaar naast het onderzoek ook nog zien en steunen. Bier, bowlen, bitterballen, wintersport triips en krokettenlunch. De tijd is eigenlijk veel te snel gegaan! Ik zou het zo weer overdoen. Laten we later samen een vakgroep oprichten!

Lieve huidige onderzoekers, ofwel de OVGO'tjes. Anna, Anneke, Charlotte, Eline, Emmy, Frederique, Inge J., Jessica, Jill, Jolijn, Jossie, Marissa F., Marissa H., Mei-an, Nienke en alle anderen. Wat een heerlijke club zijn jullie bij elkaar. Ik vind het zo leuk dat jullie net zulke vlotte gezellige borrelaars en feestvierders zijn als de

gynaika's. Graag noem ik in het bijzonder, Henrike, Marissa H. Nienke en Anneke genoemd. Wat een gezelligheid om bij jullie op de kamer te zitten.

MIJN STUDIEVRIENDEN

De mannen, Emo, Olivier, Jasper, Niels, Bram en Thom wat was het altijd gezellig met jullie. De weekendjes Friesland, de gezellige avondjes na tentamens en de feestjes op de Derkinderenstraat staan in mijn geheugen gegrift. Emo, wat ben je toch een prachtig mens, positief tot op het bot. Altijd een luisterend oor. Olivier, origineel, grappig, maar met enorme diepgang…. Je kan me na al die jaren nog steeds in de maling nemen.

Femke, wat is het toch altijd heerlijk om met jou bij te kletsen. Je bent een dierbare vriendin waar ik veel bij kwijt kan. We kennen elkaar nu sinds begin geneeskunde en hoe bijzonder is het dat dit zo heeft standgehouden. Ik gun jou en Jisk een prachtige toekomst samen.

Johan, gekke, nuchtere en humoristische kerel. We hebben samen een mooie en gezellige reis gemaakt waarbij ik je goed heb leren kennen. Je steekt jouw mening niet onder stoelen of banken. Dit waardeer ik enorm en geniet ik van. Veel plezier in het mooie Leiden met Marika.

MIJN MIDDELBARE SCHOOL VRIENDEN

Wynke, Tessa, Florentine, Maartje, Jente, JIlles en Geoffrey. Zo gezellig dat die weekendjes Zeeland nog steeds door gaan, laten we ook vooral die spontane avondjes uit in Amsterdam erin houden. Alleen Digital laat ik aan me voorbij gaan. Dank voor alle gezelligheid.

MIJN ROEIMATTIES

Aletta, Cato, Floor, Fleur, Joelle, Judith, Lotte, Maud, Minke, Nammy, Steef en Suus. Toen wij in 2010 als ploeg gingen wedstrijdroeien bij Nereus had ik niet kunnen bedenken dat we nu nog steeds zulke goede vrienden zouden zijn. Jullie zijn stuk voor stuk geweldige sociale en gezellige mensen. Onze lustrumreis was weer een eyeopener over hoe bijzonder jullie allemaal zijn. Fijn dat ik met jullie altijd overal over kan brainstormen. Ik hoop dat we nog heel veel jaren met elkaar kunnen eten, reizen, elkaar in het buitenland bezoeken, borrelen, feesten op al onze trouwerijen en roddelen.

MIJN PARANIMFEN

Jorine, wat ben jij een ontzettende lieverd en efficiënte alleskunner. Je staat altijd klaar om dingen uit te zoeken, te regelen en helpen waar nodig. Wat hebben wij een heerlijke tijd gehad. Van de tomatotimer, tot scenario's op de foto zetten. Ik hoop dat we nog heel wat jaartjes met elkaar kunnen koffieleuten.

Emo, zoals ik hierboven al heb geschreven. Wat ben je een prachtig mens, positief tot op het bot. Altijd een luisterend oor. Menig keer kreeg ik tips over hoe ik dingen goed aan kon pakken. Ik heb enorme bewondering voor jouw doorzettingsvermogen en wetenschappelijke veelzijdigheid.

MIJN BESTE VRIENDINNETJES

Merel en Christien….vanaf dat we 4 jaar oud zijn, zijn jullie er altijd voor mij geweest. De drie musketiers. Mijn getuigen bij mijn huwelijk.

Merel, creatief, doorzetter, leraar van het jaar, harde werker, idealist. Ongeacht de tijdspanne tussen de keren dat we elkaar zien. Van vroeger tot nu. Het blijft altijd goed en vertrouwd. Dat is echte vriendschap. Ik heb enorme bewondering voor jouw passie, doorzettingsvermogen en liefde voor onderwijs. Prachtig mens, blijf wie je bent.

Christien, evenwichtig, humoristisch, rots in de branding, sterk persoon, betrouwbare levensgenieter. Wat vond ik het heerlijk toen je naar Amsterdam kwam. Altijd een luisterend oor en wat hebben we geweldige tijden samen beleefd. We hebben een band die nooit kapot zal gaan. Onze gezellig jeugd heeft me gemaakt tot de persoon die ik ben. Ted en Carolien, mijn surrogaat ouders, hebben daar zeker ook een belangrijk steentje aan bijgedragen. Wat heb ik een bewondering voor jouw kijk op het leven en jouw sterke flexibele opstelling. Ik ben ontzettend trots op de persoon die je bent.

Zonder jullie zou het leven er nu heel anders uitzien.

FAMILIE

Lieve Hans, Greet en Auwerdaatjes, een leukere schoonfamilie had ik me niet kunnen wensen. Het voelt als thuiskomen.

Lieve Michiel, Myrthe, Nuri en Yanick. Mijn grote broer. Menig keer heb ik gewenst dat ik jouw talent en vlotte babbel had. Jouw vermogen om prachtige speeches voor te dragen blijft indrukwekkend. En wat een heerlijk gezin hebben jullie.

Lieve papa en mama, jullie staan altijd voor me klaar. Wat heb ik een geluk met zulke betrokken ouders. Altijd interesse, steun, luisteren en advies. Leukere, lievere ouders kan ik me niet wensen. Aan alle kanten geholpen. Zoals jullie altijd zeggen, liever met een warme hand. Nou die was en is er zeker. Ik kan mijn liefde en dankbaarheid niet omschrijven in dit kleine stukje tekst.

Mam, wat ben jij slim, scherp, een regelaar, financieel genie, intens lief, gezellig mens en altijd behulpzaam. Ik bel jou vaak als eerste als ik voor een dilemma sta, altijd een luisterend oor en altijd een passende oplossing. Mijn proefschrift heb je menig keer nagekeken. Ik weet hoeveel tijd dat kost.

Pap, wij zijn al vanaf dat ik klein ben twee handen op een buik. Verdiepende gesprekken met een goed glas wijn erbij. Samen naar de stad om een warme rookworst te halen. Jouw optimisme, never ending to do lijstje, efficiëntie en volhardende karakter zijn bewonderingswaardig en ontzettend handig. Ik kan altijd aankloppen als er iets gemaakt of ontworpen moet worden en dit wordt dan ook tot in de kleinste details secuur uitgevoerd.
Dank voor jullie eindeloze liefde en steun!

Jasper, ik kan hier een eindeloos verhaal gaan houden over hoe geweldig ik jou vind en hoe gelukkig we samen zijn, maar ik houd het kort. Woorden zijn hiervoor niet nodig.
Zonder jou had ik dit nooit kunnen voltooien. Ik verheug me op onze toekomst samen. Die wordt vast geweldig. Ik hou van je.

CURRICULUM VITAE

Geschreven door Rob en Machteld de Bruijn

Op 12 mei 1987 werd Annefleur geboren in het Juliana Ziekenhuis in Rhenen. Ze is ons tweede kind en hekkensluiter van ons gezin.
Samen met haar oudere broer Michiel groeide zij op in Veenendaal.
Ze was een dromerige lachebek die, na een aanvankelijk trage lagere school start, uitgroeide tot een veelzijdige leerlinge met een vastberaden wil om arts te worden.
Ze doorliep het Rembrandt College in Veenendaal en verbaasde ons en haar leerkrachten met steeds betere resultaten.
Annefleur heeft er hard voor moeten werken maar de wil om geneeskunde te gaan studeren heeft haar enorm gemotiveerd.

Toen ze werd uitgeloot voor geneeskunde is ze Biomedische Wetenschappen gaan studeren aan de UvA. Het jaar daarop mocht ze beginnen met de door haar zo fel begeerde studie. Ook aan de UvA.
Ze woonde op kamers in Amsterdam en verdiende bij in de thuiszorg.
Ze was lid van de studentenvereniging Mfas en actief lid van de roeivereniging Nereus waar zij deed aan wedstrijdroeien in de 4.
Tijdens haar studie ontmoette zij Jasper, nu huisarts in opleiding, met wie zij op 5 oktober 2018 trouwde en op 3 december 2018 zoon Ties Robert kreeg.

Haar verpleegstage deed zij in Suriname , een wetenschappelijke stage in Kenia [februari-juli 2011] en haar keuze coschap in Tanzania [24 juni-18 oktober 2013].
In december 2013 studeerde Annefleur af als basisarts. Ze had een grote liefde opgevat voor het continent Afrika en wilde dolgraag tropenarts worden. Om ervaring op te doen werd ze ANIOS in het Flevoziekenhuis in Almere op de afdeling gynaecologie. Helaas bleken er niet voldoende opleidingsplaatsen voor de opleiding tot tropenarts, maar in het Flevoziekenhuis kregen haar enthousiasme voor en haar interesse in de gynaecologie de overhand.

In november 2014 kreeg ze een promotieplaats in de VU en startte haar onderzoek naar “Embolisatie van Myomen en Adenomyose” onder begeleiding van prof. dr. Judith Huirne en copromotoren dr. Wouter Hehenkamp en dr. Paul Lohle.

Annefleur combineerde dit met haar werk als ANIOS en later met haar opleiding tot gynaecoloog in het Flevoziekenhuis waar zij ook begonnen is.

Annefleur, Jasper en hun prachtige zoon Ties wonen in Amsterdam.